

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 072 595 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

31.01.2001 Bulletin 2001/05

(51) Int Cl.7: **C07D 211/22, A61K 31/445,****A61P 17/04, C07D 405/06,****C07D 401/06**(21) Application number: **00304226.4**(22) Date of filing: **18.05.2000**

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

Designated Extension States:

AL LT LV MK RO SI(30) Priority: **28.05.1999 GB 9912415**

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Designated Contracting States:

**BE CH DE DK ES FI FR GR IE IT LI LU MC NL PT
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Designated Contracting States:

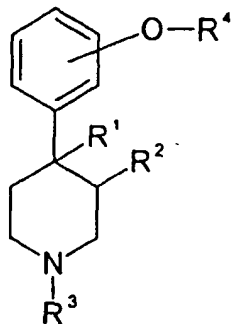
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London W1G 8ER (GB)(54) **4-arylpiperidine derivatives for the treatment of pruritus**

(57) There is provided a compound of formula I,

wherein R¹, R², R³ and R⁴ have meanings given in the description, which are useful in the prophylaxis and in the treatment of pruritus.

**EP 1 072 595 A2**

Description

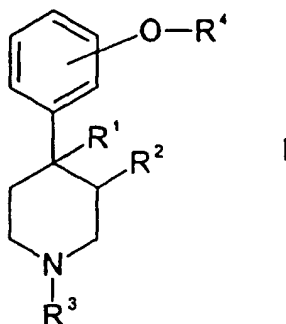
[0001] This invention relates to novel 4-phenylpiperidines having utility in the treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans, and processes for the preparation of and intermediates used in the preparation of such compounds.

[0002] Itching or pruritus is a common dermatological symptom which can give rise to considerable distress, in both humans and animals. Pruritus is often associated with inflammatory skin disease which can commonly be caused by hypersensitivity reactions, such as reaction to insect bites e.g. flea bites, or to environmental allergens such as house dust mite or pollen; or by bacterial and fungal infections of the skin or ectoparasite infections. Previous treatments for pruritus include the use of corticosteroids and antihistamines, however both have undesired side effects. Other therapies include the use of essential fatty acid dietary supplements which are slow to act and offer only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed but with limited success and there is a continuing need for an effective remedy.

[0003] Certain 1,3,4-trisubstituted 4-aryl-piperidine derivatives are disclosed in GB-A-1525584 as potent narcotic antagonists which also display analgesic properties. These compounds are also claimed in EP-B-0287339 as opioid antagonists which block the effect of agonists at the mu or kappa receptors having potential utility in treating a variety of disorders associated with these receptors such as eating disorders, opiate overdose, depression, smoking, alcoholism, sexual dysfunction, shock, stroke, spinal damage and head trauma; utility as an appetite suppressant for weight loss has also been suggested. Further related 1-N-substituted-4-aryl piperidines are disclosed in EP-A-0506468 and EP-A-0506478. Potential utility is suggested in preventing peripherally mediated undesired opiate effects and in relieving the symptoms of idiopathic constipation and irritable bowel syndrome.

[0004] According to the present invention we provide novel 4-phenylpiperidines which are potent and effective anti-pruritic agents.

[0005] Thus, the present invention provides compounds of formula I:



wherein

R¹ and R² are each independently H or C₁₋₄ alkyl;

R³ represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and -N(R^{5a})(R^{5b})), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, CN, halo, C₁₋₆ alkoxy carbonyl, C₂₋₆ alkanoyl, C₂₋₆ alkanoyloxy, C₃₋₈ cycloalkyl, C₄₋₉ cycloalkanoyl, N(R^{6a})S(O)₂R⁷, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A¹-N(R^{6b})(R^{6c});

n is 0, 1 or 2;

W represents a single bond, C(O) or S(O)_p;

A¹ represents a single bond or C₁₋₁₀ alkylene;

provided that when both W and A¹ represent single bonds, then the group -N(R^{6b})(R^{6c}) is not directly attached to an unsaturated carbon atom;

p is 0, 1 or 2;

R^{5a} to R^{5d} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphe-

nyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het²;

provided that R^{5d} does not represent H when n represents 1 or 2;

R^{6a} to R^{6c} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het³, or R^{6b} and R^{6c} together represent unbranched C₂₋₆ alkylene which alkylene group is optionally interrupted by O, S and/or an N(R⁸) group and is optionally substituted by one or more C₁₋₄ alkyl groups;

R⁷ represents C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, OH, nitro, amino or halo;

R⁸ represents H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, A²-(C₃₋₈ cycloalkyl) or A²-aryl;

A² represents C₁₋₆ alkylene;

Het¹, Het² and Het³ independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms); and

R⁴ represents H, C₁₋₅ alkyl, C₁₋₁₂ alkanoyl, (pyridin-3-yl)carbonyl or (pyridin-4-yl)carbonyl (which latter two groups are optionally in the pyridine N-oxide form);

or pharmaceutically, or veterinarily, acceptable derivatives thereof;

provided that, when the group OR⁴ is attached to the benzene ring at the *meta*-position relative to the piperidine ring and the piperidine is not in the N-oxide form, then:

(a) when R¹ and R² both represent C₁₋₄ alkyl, then R³ does not represent: - C₁₋₈ alkyl (optionally terminally substituted by C₄₋₈ cycloalkyl);

unsubstituted C₃₋₈ alkenyl;

unsubstituted C₃₋₈ alkynyl;

C₁₋₃ alkyl, terminally substituted by phenyl, phenoxy, -S-phenyl, -N(H)-phenyl or -N(C₁₋₄ alkyl)-phenyl, furan-2-yl or thiophen-2-yl; C₁₋₄ alkyl, terminally substituted by an OH group and a further group selected from phenyl, furan-2-yl and thiophen-2-yl; or

C₃₋₅ alkenyl, terminally substituted by phenyl, furan-2-yl or thiophen-2-yl, where the position of unsaturation is at the carbon atoms that are α, β to the phenyl, furan-2-yl or thiophen-2-yl group;

all of which phenyl, phenoxy and phenylthio groups are optionally substituted by one or two substituents selected from OH, C₁₋₃ alkyl, C₁₋₃ alkoxy, halo, nitro, amino and CF₃; and

all of which furanyl and thiophenyl groups are optionally substituted by a methyl group; and

(b) when R¹ represents methyl, and:-

(i) R² represents C₁₋₄ alkyl and R⁴ represents H or C₁₋₄ alkanoyl, then R³ does not represent:-

unsubstituted C₃₋₈ alkyl;

unsubstituted C₄₋₈ alkenyl;

C₃₋₆ alkyl, substituted by an unsubstituted C₄₋₈ cycloalkyl group;

C₂ alkyl, terminally substituted by an unsubstituted C₅₋₉ cycloalkanoyl, an unsubstituted C₂₋₆ alkanoyl group or an unsubstituted thiophenyl group;

C₄₋₉ alkyl (optionally substituted at 4- to 9-C position by C₄₋₈ cycloalkyl) or C₅₋₉ alkenyl, which alkyl or alkenyl groups are substituted at the 3-C position by OH, C₁₋₆ alkoxy, oxy-C₁₋₃-alkylphenyl or C₂₋₅ alkanoyloxy (which latter three groups are all unsubstituted); or

C₃ alkyl, terminally substituted by (1) OH, C₁₋₆ alkoxy, oxy-C₁₋₃-alkylphenyl or C₂₋₅ alkanoyloxy (which latter three groups are all unsubstituted) and (2) C₄₋₈ cycloalkyl, thiophenyl (which latter two groups are both unsubstituted); or

(ii) R² represents H or C₁₋₄ alkyl and R⁴ represents H or C₁₋₅ alkyl, then

(I) R³ does not represent:-

methyl;

C₂₋₁₀ alkyl or C₄₋₁₀ alkenyl, both of which are substituted at the 2-, 3- or 4-C position by -W-A¹-N(R^{6b})(R^{6c}) and which alkyl group only is also optionally substituted at the 3- to 10-C, 4- to 10-C or 5- to 10-C position (respectively) by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl; or

C₁₋₄ alkyl, which alkyl group is terminally substituted by -W-A¹-N(R^{6b})(R^{6c}), and is also optionally terminally substituted by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl;

in which, in both cases, W is a single bond, A¹ is a single bond or C₁₋₃ alkylene, R^{6b} or R^{6c} is H or unsubstituted C₁₋₁₀ alkyl and R^{6b} or R^{6c} (as appropriate) is H, C₃₋₈ cycloalkyl, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, phenyl or C₁₋₃ alkylphenyl (which latter five groups are all unsubstituted); or

(II) R³ does not represent:-

C₁₋₁₀ alkyl or C₃₋₁₀ alkenyl, both of which are substituted at the 1- to 5-C (as appropriate) by unsubstituted C₁₋₆ alkoxy carbonyl or W-A¹-N(R^{6b})(R^{6c}) and which alkyl or alkenyl groups are also optionally substituted at the 2- to 10-C, 3- to 10-C, 4- to 10-C or 5- to 10-C position (respectively) by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl; or

C₁₋₅ alkyl, which alkyl group is terminally substituted by an unsubstituted C₁₋₆ alkoxy carbonyl group or -W-A¹-N(R^{6b})(R^{6c}), and is optionally terminally substituted by unsubstituted phenyl or unsubstituted C₃₋₈ cycloalkyl;

in which, in both cases, W is -C(O)-, A¹ is a single bond, R^{6b} or R^{6c} is H or unsubstituted C₁₋₃ alkyl and R^{6b} or R^{6c} (as appropriate) is H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₈ cycloalkyl, phenyl, C₁₋₃ alkylphenyl (which latter five groups are all unsubstituted), linear C₁₋₄ alkyl (which latter group is terminally substituted by amino), or R^{6b} and R^{6c} together represent unsubstituted C₃₋₅ alkylene;

(c) when R¹ and R² both represent methyl and are in the mutually *trans*-configuration and R⁴ represents H or C₁₋₄ alkanoyl, then R³ does not represent:- unsubstituted C₁₋₈ alkyl;

unsubstituted C₃₋₈ alkenyl;

unsubstituted C₃₋₈ alkynyl;

C₁₋₆ alkyl, terminally substituted by an unsubstituted C₃₋₈ cycloalkyl group; C₁₋₃ alkyl, terminally substituted by C₃₋₈ cycloalkoxy, C₃₋₈ cycloalkoxy, C₃₋₈ cycloalkyl, naphthyl, thiophenyl, thiophenoxy, furanyl, furanoxy, tetrahydrofuranyl, pyridinyl or pyridinyloxy (which latter eleven groups are all unsubstituted), phenyl or phenoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy); or

C₁₋₄ alkyl, terminally substituted by an OH group and by one of the following groups: phenyl (which latter group is optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy), C₁₋₂ alkylphenyl, C₃₋₈ cycloalkyl, thiophenyl, furanyl or pyridinyl (which latter four groups are all unsubstituted);

in all of which provisos, optionally substituted alkyl, alkenyl and alkynyl groups are not interrupted by one or more O and/or S atoms;

which compounds are referred to together hereinafter as "the compounds of the invention".

[0006] In the definitions used herein, alkyl, alkylene, alkoxy, alkoxy carbonyl, alkanoyl, alkanoyloxy, alkenyl, alkynyl and the alkyl parts of alkylphenyl and aryl alkoxy groups may, when there is a sufficient number of carbon atoms, be straight or branched-chain and/or optionally interrupted by one or more oxygen and/or sulfur atom(s). The term halo includes fluoro, chloro, bromo or iodo. The term "aryl" includes optionally substituted phenyl, naphthyl and the like, and "aryloxy" includes optionally substituted phenoxy and naphthyloxy and the like. Unless otherwise specified, aryl and aryloxy groups are optionally substituted by one or more (e.g. one to three) substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy carbonyl and C₁₋₅ alkanoyl (which latter four groups are optionally substituted by one or more halo atoms).

[0007] The heterocyclic rings that Het¹, Het² and Het³ represent may be fully saturated, partially unsaturated and/or wholly or partially aromatic in character. Specific rings that may be mentioned include: for Het¹, dioxane, dioxolane, morpholine, piperidine, perhydroazepine, pyrazole, pyridine, triazole, tetrahydrofuran, tetrahydropyran, pyrrole, pyrrolidine or tetrazole; for Het², tetrahydropyran.

[0008] For the avoidance of doubt, when Het (Het¹, Het² and Het³) groups are at least part-saturated, possible points of substitution include the atom (e.g. the carbon atom) at the point of attachment of the Het group to the rest of the molecule. Het groups may also be attached to the rest of the molecule via a heteroatom.

[0009] The piperidine moiety in compounds of formula I may be in N-oxidised form. Sulfur atoms that may interrupt (e.g. alkyl) substituents in compounds of formula I may be present in oxidised form (e.g. as sulfoxides or sulfones). All Het¹, Het² and Het³ groups may also be in N- or S-oxidized forms.

[0010] The term "pharmaceutically, or veterinarily, acceptable derivatives" includes non-toxic salts. Salts which may be mentioned include: acid addition salts, for example, salts formed with sulfuric, hydrochloric, hydrobromic, phosphoric, hydroiodic, sulfamic, organo-sulfonic, citric; carboxylic (e.g. acetic, benzoic, etc.), maleic, malic, succinic, tartaric, cinnamic, ascorbic and related acids; base addition salts; salts formed with bases, for example, the sodium, potassium and C₁₋₄ alkyl ammonium salts.

[0011] The compounds of the invention may also be in the form of quaternary ammonium salts, e.g. at the piperidine moiety, which salts may be formed by reaction with a variety of alkylating agents, such as an alkyl halide or an ester of sulfuric, or an aromatic sulfonic acid.

[0012] The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formula I are included within the scope of the invention.

[0013] The compounds of the invention contain one or more asymmetric centres and thus they can exist as enantiomers and diastereomers. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techniques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. The invention includes the use of both the separated individual isomers as well as mixtures of isomers.

[0014] Also included within the scope of the invention are radiolabelled derivatives of compounds of formula I which are suitable for biological studies.

[0015] According to a further aspect of the invention, there is provided a compound of formula I, as hereinbefore defined, with the additional proviso that when OR⁴ is OH, and is attached to the benzene ring at the *meta*-position relative to the piperidine ring, which piperidine ring is not in N-oxidised form, then R³ represents:

optionally substituted aryl;

optionally substituted C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl (which two groups are both interrupted by at least one oxygen and/or sulfur atoms);

C₂₋₁₀ alkyl, interrupted by at least two oxygen atoms and/or at least one sulfur atom;

C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl, which groups are all optionally interrupted by one or more oxygen and/or sulfur atoms, and are substituted and/or terminated by one or more of:

S(O)_nR^{5d}, N(R^{6a})S(O)₂R⁷, Het¹ (substituted by one or more substituents selected from nitro, amino and C₁₋₅ alkanoyl (which latter group is optionally substituted by one or more halo atoms)), aryl (substituted by one or more substituents selected from nitro, amino and C₁₋₅ haloalkanoyl) or adamantyl (which latter group is substituted by one or more of the relevant substituents identified hereinbefore); or

OR^{5c}, in which R^{5c} represents C₇₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl or Het² (which latter four groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore), or R^{5c} represents C₁₋₁₀ alkyl, C₁₋₄ alkylphenyl, C₃₋₈ cycloalkyl or aryl (which latter four groups are all substituted by one or more of the relevant substituents identified hereinbefore);

-W-A¹-N(R^{6b})(R^{6c}), in which R^{6b} and/or R^{6c} independently represent C₁₋₄ alkylphenyl (which latter group is optionally substituted by one or more of the relevant substituents identified hereinbefore), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl (which latter four groups are all substituted by one or more of the relevant substituents identified hereinbefore), or aryl (substituted by one or more substituents selected from nitro, amino and C₁₋₅ haloalkanoyl);

which compounds may also be termed "compounds of the invention".

[0016] According to a further aspect of the invention, there is provided a compound of formula I, as hereinbefore defined, with the additional proviso that when OR⁴ is O-C₁₋₄ alkyl, and is attached to the benzene ring at the *meta*-position relative to the piperidine ring, which piperidine ring is not in N-oxidised form, then R³ does not represent: straight or branched-chain C₁₋₁₀ alkyl (optionally substituted by one or more substituents selected from unsubstituted aryl or unsubstituted C₃₋₈ cycloalkyl);

which compounds may also be termed "compounds of the invention".

[0017] Preferred compounds of the invention include those wherein:

The group OR⁴ is attached to the benzene ring in the position *meta*-relative to the piperidine group;

R¹ represents C₁₋₂ alkyl;

R² represents H or C₁₋₂ alkyl;

R³ represents aryl (optionally substituted by one or more substituents selected from C₁₋₂ alkyl, C₁₋₂ alkoxy, halo, nitro and -N(R^{5a})(R^{5b})), C₁₋₈ alkyl, C₃₋₈ alkenyl or C₃₋₈ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally interrupted by one or more oxygen atoms and/or are substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, CN, halo, C₁₋₄ alkoxy carbonyl, C₄₋₆ cycloalkyl, C₅₋₇ cycloalkanoyl, Het¹, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C₁₋₂ alkyl, C₁₋₂ alkoxy or halo), or -W-A¹-N(R^{6b})(R^{6c});

W represents a single bond or C(O);

A¹ represents a single bond or C₁₋₃ alkylene;

R^{5a} to R^{5d} each independently represent H, C₁₋₆ alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, C₄₋₈ cycloalkyl, C₁₋₂ alkylphenyl, aryl or Het²;

R^{6b} and R^{6c} independently represent H, C₁₋₂ alkyl, Het³, or R^{6b} and R^{6c} together represent unbranched C₂₋₆ alkylene which alkylene group is optionally interrupted by O or S and is optionally substituted by one or more C₁₋₂ alkyl groups;

Het¹, Het² and Het³ independently represent 5- to 7-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O and C₁₋₂ alkyl (which latter group is optionally substituted by one or more halo atoms);

R⁴ represents H or C₁₋₅ alkanoyl.

[0018] More preferred compounds of the invention include those wherein:

R¹ represents methyl;

R² represents H or methyl;

R³ represents phenyl (optionally substituted by one or more substituents selected from methyl, methoxy and -N(CH₃)₂), linear C₁₋₇ alkyl or linear C₁₋₇ alkenyl, which alkyl or alkenyl groups are optionally interrupted by one or more oxygen atoms and/or are optionally substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, C₁₋₂ alkoxy carbonyl, C₄₋₆ cycloalkyl, Het¹ or -C(O)N(R^{6b})(R^{6c});

R^{5c} and R^{5d} each independently represent H, C₁₋₃ alkyl, C₃₋₄ alkenyl, C₅₋₇ cycloalkyl, phenyl, naphthyl or Het²;

R^{6b} and R^{6c} together represent unbranched C₄₋₆ alkylene which alkylene group is optionally interrupted by O and is optionally substituted by one or more C₁₋₂ alkyl groups;

Het¹ and Het² independently represent 5- to 7-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, and which groups are optionally substituted by one or more C₁₋₂ alkyl groups.

[0019] Particularly preferred compounds of the invention include those wherein:

R¹ and R² represent methyl groups in the mutually *trans* configuration;

R⁴ represents H.

[0020] Preferred compounds of the invention include the compounds of the Examples described hereinafter.

[0021] Thus, according to a further aspect of the invention, there is provided a compound of formula I which, irrespective of any of the foregoing definitions and/or provisos, is:

(±)-3-[1-[2-(cyclohexyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[2-(1,3-dioxan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-(3-hydroxypropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[3-(allyloxy)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-(2-ethoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-(3-tetrahydro-3-furanylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[2-(2-methoxyethoxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-(2-methoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[2-(vinylloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[2-[2-(2-hydroxyethoxy)ethoxy]ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[3-(tetrahydro-2H-pyran-2-yloxy)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-(3-tetrahydro-2H-pyran-2-ylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;

(±)-3-[1-[3-(1,3-dioxan-2-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(3,3-dimethoxypropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(2-hydroxyethoxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(1,3-dioxolan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 5 (±)-3-[1-[4-(1,3-dioxolan-2-yl)butyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(5-hydroxypentyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(3-tetrahydro-2*H*-pyran-4-ylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 10 (±)-3-[1-[2-(2-naphthyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(2-isopropoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 3-[1-(2-propoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(cyclopentyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(3-tetrahydro-2-furanylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol;
 15 (±)-3-[1-[2-(cyclohexylsulfanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(ethylsulfanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(ethylsulfinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[2-(ethylsulfonyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[3-(1*H*,2,3,4-tetrazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 20 (±)-3-[1-[3-(1*H*-pyrazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[3-(4-pyridinyl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[3-(1*H*,2,4-triazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-[3-(1*H*-pyrrol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-1-(4-morpholinyl)-1-propanone;
 25 3-[1-[3-(4-morpholinyl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 3-[1-[2-(1-azepanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 3-[1-[2-(4-morpholinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 3-[1-[2-(1-piperidinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 3-[1-[2-(1-pyrrolidinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 30 3-[1-[3-(1-piperidinyl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol;
 (±)-3-[1-(3-methoxyphenyl)-*trans*-3,4-dimethylpiperidinyl]phenol; or
 (±)-3-[1-[4-(dimethylamino)phenyl]-*trans*-3,4-dimethylpiperidinyl]phenol; or
 (±)-methyl 3-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]propionate,

35 which compounds may also be termed "compounds of the invention".

[0022] According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

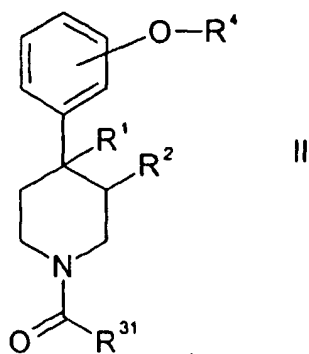
[0023] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

40 1. Compounds of formula I wherein R³ represents C₁ alkyl optionally substituted by C₃₋₈ cycloalkyl, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R³ represents C₂₋₁₀ alkyl, C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore in respect of R³), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom via a CH₂ group, wherein Het¹ is as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula II,

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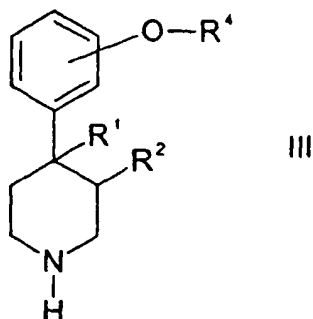
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wherein R^{31} represents H, C_{3-8} cycloalkyl, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{5c} , $S(O)_nR^{5d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{6a})S(O)_2R^7$, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{6b})(R^{6c})$, and R^1 , R^2 , R^4 , R^{5c} , R^{5d} , R^{6a} to R^{6c} , R^7 , Het¹, n, W and A^1 are as hereinbefore defined, using a suitable reducing agent (e.g. lithium aluminium hydride or a borane derivative), for example as described hereinbefore.

Compounds of formula II may be prepared by reaction of a corresponding compound of formula III,



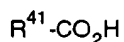
wherein R^1 , R^2 and R^4 are as hereinbefore defined with a compound of formula IV,



or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or anhydride), wherein R^{31} is as hereinbefore defined, using coupling conditions known to those skilled in the art.

Compounds of formula III may be prepared from appropriate precursors by analogy with other methods disclosed herein that describe the production of compounds of formula I.

2. Compounds of formula I in which R^4 represents C_{1-12} alkanoyl, (pyridin-3-yl)carbonyl or (pyridin-4-yl)carbonyl (which latter two groups are optionally in the pyridine N-oxide form) may be prepared by reaction of a corresponding compound of formula I in which R^4 represents H with a compound of formula V,



V

or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or anhydride), wherein R^{41} represents C_{1-11} alkyl, pyridin-3-yl or pyridin-4-yl (which latter two groups are optionally in the pyridine N-oxide form), using coupling conditions known to those skilled in the art.

3. Compounds of formula I may also be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a compound of formula VI,



VI

wherein L^1 represents a leaving group such as halo, alkanesulfonate, perfluoroalkanesulfonate or arenesulfonate) and R^3 is as hereinbefore defined, under conditions that are well known to those skilled in the art, which include, for example, alkylation at between room temperature and reflux temperature in the presence of a reaction-inert organic solvent (e.g. *N,N*-dimethylformamide) and a suitable base (e.g. $NaHCO_3$), and arylation at between room temperature and reflux temperature in the presence of a suitable catalyst system (e.g. tris(dibenzylideneacetone) palladium(0) combined with tri-*o*-tolylphosphine), an appropriate strong base (e.g. sodium *tert*-butoxide) and a reaction-inert solvent (e.g. toluene).

4. Compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31} , wherein R^{31} is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a compound of formula VII,



VII

wherein R^{31} is as hereinbefore defined, for example in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyanoborohydride or sodium triacetoxymethylborohydride) and an appropriate solvent (e.g. methanol).

5. Compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{5d}$, $S(O)_2R^{5d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{6b})(R^{6c})$, $-S(O)-A^1-N(R^{6b})(R^{6c})$, or $-S(O)_2-A^1-N(R^{6b})(R^{6c})$, wherein R^{5d} , R^{6b} , R^{6c} and A^1 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula III, as hereinbefore defined, with a compound of formula VIII,



VIII

wherein R^{3a} represents R^3 as hereinbefore defined except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{5d}$, $S(O)_2R^{5d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{6b})(R^{6c})$, $-S(O)-A^1-N(R^{6b})(R^{6c})$ or $-S(O)_2-A^1-N(R^{6b})(R^{6c})$, wherein R^{5d} , R^{6b} , R^{6c} and A^1 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF).

Compounds of formulae IV to IX, and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions (see, for example, "Comprehensive Organic Transformations - A Guide to Functional Group Preparations", R. C. Larrock, VCH (1989), or "Advanced Organic Chemistry - Reactions, Mechanism and Structure", 4th edition, J. March, Wiley-Interscience (1992)). For example, compounds of formula I in which R^4 represents H may be made according to or by analogy with the procedures disclosed in the publications mentioned above relating to 4-arylpiperidine-based compounds.

[0024] Substituents on alkyl, heterocyclic and aryl groups in the above-mentioned compounds may also be intro-

duced, removed and interconverted, using techniques which are well known to those skilled in the art. For example, nitro may be reduced to amino, OH may be alkylated to give alkoxy, alkoxy may be hydrolysed to OH, alkenes may be hydrogenated to alkanes, halo may be hydrogenated to H, etc.

[0025] The skilled person will also appreciate that other various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I.

[0026] The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

[0027] It will be appreciated by those skilled in the art that, in the course of carrying out the processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

[0028] Functional groups which it is desirable to protect include oxo, OH, amino and carboxylic acid. Suitable protective groups for oxo include acetals, ketals (e.g. ethylene ketals) and dithianes. Suitable protective groups for OH include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protective groups for amino include *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protective groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters. Suitable protective groups for terminal alkynes include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl).

[0029] The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

[0030] Protective groups may be removed in accordance with techniques which are well known to those skilled in the art.

[0031] The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

[0032] Persons skilled in the art will also appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

[0033] It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

[0034] It will be further appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described in 'Design of Prodrugs' by H. Bundgaard, Elsevier, 1985 (the disclosure in which document is hereby incorporated by reference), may be placed on appropriate functionalities, when such functionalities are present within compounds of formula I.

[0035] All protected derivatives, and prodrugs, of compounds of formula I are included within the scope of the invention.

[0036] Pharmaceutically acceptable acid addition salts of the compounds of formula I which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula I with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

[0037] The above procedures may be adapted as appropriate to the particular reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples provided hereafter to enable all of the compounds of formula I to be prepared.

[0038] The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals including humans. They are therefore indicated as pharmaceuticals and, in particular, for use as animal medicaments.

[0039] According to a further aspect of the invention there is provided the compounds of the invention (optionally a compound of formula I as defined herein but without the provisos) for use as medicaments, such as pharmaceuticals

and animal medicaments.

[0040] By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

[0041] In particular, the compounds of the invention have been found to be useful in the treatment of pruritus, and conditions characterised by pruritus as a symptom.

5 [0042] Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention (optionally a compound of formula I as defined herein but without the provisos) in the manufacture of a medicament for the treatment of pruritus or a medical condition characterised by pruritus as a symptom.

[0043] The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and conditions
10 which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

[0044] Thus, the invention provides a method of treating or preventing pruritus or a medical condition characterised by pruritus as a symptom in an animal (e.g. a mammal), which comprises administering a therapeutically effective amount of a compound of the invention (optionally a compound of formula I as defined herein but without the provisos) to an animal in need of such treatment.

15 [0045] The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

20 [0046] While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

25 [0047] The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

[0048] The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

35 [0049] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

40 [0050] In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

45 [0051] For veterinary use, the compounds of the invention are of particular value for treating pruritus in domestic animals such as cats and dogs and in horses.

[0052] As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

[0053] For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet,
50 capsule and ointment preparations which are formulated in accordance with standard pharmaceutical practice.

[0054] Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of illustration and should not be construed as limiting) include antiparasitics, e.g. fipronil, lufenuron, imidacloprid, avermectins (e.g. abamectin, ivermectin, doramectin), milbemycins, organophosphates, pyrethroids; antihistamines, e.g. chlorpheniramine, trimetoprim, diphenhydramine, doxylamine; antifungals, e.g. fluconazole, ketoconazole, itraconazole, griseofulvin, amphotericin B; antibacterials, e.g. enrofloxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammatories e.g. prednisolone, betamethasone, dexamethasone, carprofen, ketoprofen; dietary supplements, e.g. gamma-linoleic acid; and emollients. Therefore, the invention further provides a
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product containing a compound of the invention and a compound from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of pruritus.

[0055] The skilled person will also appreciate that compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

[0056] Thus, according to a further aspect of the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention (optionally a compound of formula I as defined herein but without the provisos) in admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

[0057] Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

[0058] The biological activity of the compounds of the present invention was determined by the following test method.

Biological Test

[0059] The compounds of the invention are evaluated for their activity as antipruritic agents by measuring their ability to inhibit the hind leg scratching behaviour induced in rats by the administration of a known pruritogenic agent. These studies are based on the procedure described by Berendsen and Broekkamp in the European Journal of Pharmacology, 1991, 194, 201. The test is performed as follows:

Male Wistar rats (approximately 150 g body weight) are challenged with a pruritogen by subcutaneous injection of 5-methoxytryptamine hydrochloride (4 mg/3 mL/kg) dissolved in physiological saline into the scruff of the neck. At this dose a constant and quantifiable hindleg scratching response lasting up to 90 minutes is obtained.

The test compound is administered to the test animals by subcutaneous injection in an aqueous micelle formulation.

The test compound is prepared in the following manner. The compound is dissolved in a vehicle (composition v/v%: glycerol formal, 24; tween 80, 17; benzyl alcohol, 1.5 and purified water to 100) then seven parts purified water is added to three parts of the above vehicle to give the aqueous micelle formulation. The compounds can be administered pre- or post-challenge or may be administered at the same time as the pruritogenic challenge.

After the pruritogen challenge has been administered, hindleg scratching is scored for each animal by recording the presence or absence of scratching during each 30 second interval as 1 or 0 scored respectively. The score for each animal is totalled after 25 minutes (maximum score 50). The efficacy of compounds is assessed by their ability to significantly reduce the score in treated groups compared to the control group.

[0060] The invention is illustrated by the following Preparations and Examples in which the following abbreviations may be used:

APCI = atmospheric pressure chemical ionisation

br (in relation to NMR) = broad

DCM = dichloromethane

DMF = *N,N*-dimethylformamide

DMSO = dimethylsulfoxide

d (in relation to time) = day

d (in relation to NMR) = doublet

dd (in relation to NMR) = doublet of doublets

EtOAc = ethyl acetate

EtOH = ethanol

h = hour(s)

m (in relation to NMR) = multiplet

MeOH = methanol

min = minute

q (in relation to NMR) = quartet

rt = room temperature

s (in relation to NMR) = singlet

t (in relation to NMR) = triplet

THF = tetrahydrofuran

TSI = thermospray ionisation

[0061] When column chromatography is referred to this usually refers to a glass column packed with silica gel (40-63 μ m). Pressure of about 165 kPa is generally applied and the ratio of crude product : silica gel required for purification is typically 50:1. Alternatively, an Isolute™ SPE (solid phase extraction) column or Waters Sep-Pak™ cartridge packed

with silica gel may be used under atmospheric pressure. The ratio of crude product to silica gel required for purification is typically 100:1.

[0062] Hydrochloride salts of the compounds of the examples may be made by methods known to those skilled in the art of synthetic chemistry. For example, ethereal hydrochloric acid (1.0 M, 1.2 equivalent) may be added to a solution of free base in dichloromethane (1 g : 100 mL), the excess solvent decanted off and the remaining precipitate washed three times with ether and dried *in vacuo*.

[0063] A common starting material, (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol, can be prepared using the procedures described in: a) Zimmerman et al, *J. Org. Chem.*, 1991, **56**, 1660; b) Werner et al, *J. Org. Chem.*, 1996, **61**, 587-597. All starting materials were obtained from commercial sources unless stated otherwise.

[0064] Nuclear magnetic resonance (NMR) spectral data were obtained using a Bruker AC3000, AM300 or AM400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. ¹H-NMR data are measured in solution in CDCl₃ unless otherwise specified. Mass spectral (MS) data were obtained on a Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000 spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

Examples

Example 1: (±)-3-[1-[2-(Cyclohexyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0065] To a solution of 2-(cyclohexyloxy)ethyl-4-methylbenzenesulfonate (Preparation 18, 226 mg, 0.76 mmol) in toluene (2.0 mL) at 0°C under a nitrogen atmosphere was added pyridine (101 mg, 1.28 mmol) and (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (155 mg, 0.76 mmol). The reaction was heated at reflux for 3 hours and then at room temperature for 48 hours. The mixture was concentrated *in vacuo* and the crude residue was partitioned between a saturated aqueous sodium hydrogencarbonate solution (10 mL) and ethyl acetate (10 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a crude yellow oil. This was purified using a preparative silica plate, eluting with dichloromethane : methanol (95:5), to give the title compound (79 mg, 31 %) as a colourless oil.

¹H-NMR (d, 3H), 1.10-1.24 (m, 6H), 1.25 (s, 3H), 1.55 (m, 1H), 1.60-1.68 (m, 2H), 1.71-1.95 (m, 2H), 2.05 (m, 1H), 2.35 (m, 1H), 2.60-2.92 (m, 5H), 3.05 (m, 1H), 3.25 (m, 1H), 3.68 (t, 2H), 6.68 (d, 1H), 6.78-6.83 (m, 2H), 7.11 (t, 1H). MS (ESI⁺) : *m/z* [MH⁺] 332.5; C₂₁H₃₃NO₂ + H requires 332.3

Example 2: (±)-3-[1-[2-(1,3-Dioxan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0066] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (100 mg, 0.49 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature under a nitrogen atmosphere was added sodium hydrogencarbonate (54 mg, 0.54 mmol) and 2-(2-bromoethyl)-1,3-dioxane (107 mg, 0.55 mmol). The solution was heated at reflux for 1 hour, cooled and then poured into a saturated sodium hydrogencarbonate solution (10 mL) and extracted with diethyl ether (4 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a brown oil. This was purified by column chromatography on silica gel (10 g), eluting with a gradient of dichloromethane : ethanol : 0.88 ammonia (200:8:1 to 100:8:1), to give the title compound (110 mg, 64%) as a colourless oil.

¹H-NMR : 0.78 (d, 3H), 1.28 (s, 3H), 1.35 (m, 1H), 1.60 (m, 1H), 1.72-2.20 (m, 4H), 2.25-2.60 (m, 6H), 2.85 (m, 1H), 3.68-3.78 (m, 2H), 4.02-4.12 (m, 2H), 4.60 (t, 1H), 6.65 (m, 1H), 6.75 (m, 1H), 6.81 (d, 1H), 7.15 (t, 1H).

MS (ESI⁺) : *m/z* [MH⁺] 320.0; C₁₉H₂₉NO₃ + H requires 320.2.

Example 3: (±)-3-[1-(3-Hydroxypropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0067] To a stirred solution (±)-methyl 3-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]propionate (Example 45, 117 mg, 0.40 mmol) in tetrahydrofuran (1 mL) at 0°C was added lithium aluminium hydride (1.0 M solution in THF, 1.2 mL, 1.2 mmol). After 1 hour the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product. This was purified by column chromatography on silica gel, eluting with a gradient of methanol : dichloromethane : 0.880 ammonia (10:990:1 to 30:970:3), to give the title compound (32 mg, 12%) as a pale yellow oil.

¹H-NMR (C₆D₆) : 0.69 (d, 3H), 1.06 (s, 3H), 1.21-1.36 (m, 3H), 1.63 (m, 1H), 1.82 (m, 1H), 2.05-2.20 (m, 4H), 2.36 (m, 1H), 2.56 (m, 1H), 3.71 (t, 2H), 6.59 (m, 1H), 6.82 (m, 1H), 6.86 (m, 1H), 7.05-7.10 (m, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 264.2; C₁₆H₂₅NO₂ + H requires 264.2

Example 4: (±)-3-[1-[3-(Allyloxy)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0068] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 3-allyloxypropyl chloride (43 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (58 mg, 66%) as its acetate salt.

¹H-NMR (selected data from the acetate salt) : 0.78 (d, 3H), 1.28 (s, 3H), 1.60 (m, 1H), 1.78-1.90 (m, 2H), 3.45 (t, 2H), 3.91 (m, 2H), 5.14 (t, 1H), 5.23 (d, 1H), 5.85 (m, 1H), 6.61 (d, 1H), 6.70-6.81 (m, 2H), 7.10 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 304.5; C₁₉H₂₉NO₂ + H requires 304.2.

Example 5: (±)-3-[1-(2-Ethoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0069] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 2-bromoethyl ethyl ether (50 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (31 mg, 39%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.82 (d, 3H), 1.18 (t, 3H), 1.30 (s, 3H), 1.70 (m, 1H), 2.01 (s, 3H), 2.05 (m, 1H), 2.38 (m, 1H), 2.81-3.05 (m, 5H), 3.20 (m, 1H), 3.42 (q, 2H), 3.68 (t, 2H), 6.65 (d, 1H), 6.72-6.80 (m, 2H), 7.12 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 278.5; C₁₇H₂₇NO₂ + H requires 278.2.

Example 6: (±)-3-[1-(3-Tetrahydro-3-furanylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0070] To a stirred solution of (±)-1-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(tetrahydro-3-furanyl)-1-propanone (Preparation 2, 150 mg, 0.47 mmol) in tetrahydrofuran (25 mL) at room temperature was added lithium aluminium hydride (2.2 mL, 1.0 M solution in diethyl ether). After 10 minutes, the reaction mixture was quenched with water and the resulting precipitate was removed by filtration through a pad of Celite®, washing with diethyl ether. The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product (150 mg, 100%).

¹H-NMR : 0.77 (d, 3H), 1.27 (s, 3H), 1.32-1.61 (m, 6H), 1.92-2.03 (m, 2H), 2.18 (m, 1H), 2.22-2.41 (m, 4H), 2.46-2.58 (m, 2H), 2.82 (m, 1H), 3.30 (t, 1H), 3.73 (m, 1H), 3.81 (m, 1H), 3.88 (t, 1H), 6.59 (d, 1H), 6.71 (s, 1H), 6.80 (d, 1H), 7.10 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 318.5; C₂₀H₃₁NO₂ + H requires 318.2.

Example 7: (±)-3-[1-[2-(2-Methoxyethoxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0071] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 1-bromo-2-(2-methoxyethoxy)ethane (59 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (71 mg, 80%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.82 (d, 3H), 1.35 (s, 3H), 1.72 (m, 1H), 2.03-2.10 (m, 4H), 2.38 (m, 1H), 2.81-3.13 (m, 6H), 3.40 (s, 3H), 3.50-3.63 (m, 4H), 3.70-3.78 (m, 2H), 6.68 (m, 1H), 6.81-6.82 (m, 2H), 7.18 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 308.3; C₁₈H₂₉NO₃ + H requires 308.2.

Example 8: (±)-3-[1-(2-Methoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0072] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 1-bromo-2-methoxyethane (45 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then added water (10 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered

and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (17 mg, 22%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.83 (d, 3H), 1.35 (s, 3H), 1.72 (m, 1H), 2.03-2.09 (m, 4H), 2.38 (m, 1H), 2.70-3.18 (m, 6H), 3.38 (s, 3H), 3.58-3.65 (m, 2H), 6.68 (d, 1H), 6.79-6.84 (m, 2H), 7.18 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 264.2; C₁₆H₂₅NO₂ + H requires 264.2.

Example 9: (±)-3-[1-[2-(Vinylloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0073] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 2-chloroethyl vinyl ether (34 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (13 mg, 16%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.82 (d, 3H), 1.38 (s, 3H), 1.62 (m, 1H), 2.00-2.08 (m, 4H), 2.37 (m, 1H), 2.56-3.05 (m, 6H), 3.80-3.92 (m, 2H), 4.02 (d, 1H), 4.20 (d, 1H), 6.47 (dd, 1H), 6.65 (d, 1H), 6.79 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 276.3; C₁₇H₂₅NO₂ + H requires 276.2.

Example 10: (±)-3-[1-[2-[2-(2-Hydroxyethoxy)ethoxy]ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0074] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 2-[2-(2-chloroethoxy)ethoxy]ethanol (54 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (35 mg, 36%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.85 (d, 3H), 1.35 (s, 3H), 1.70 (m, 1H), 2.01-2.10 (m, 4H), 2.32 (m, 1H), 2.70-2.90 (m, 5H), 3.10 (m, 1H), 3.58-3.70 (m, 6H), 3.71-3.79 (m, 4H), 6.68 (d, 1H), 6.79-6.83 (m, 2H), 7.18 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 338.4; C₁₉H₃₁NO₄ + H requires 338.2.

Example 11: (±)-3-[1-[3-(Tetrahydro-2H-pyran-2-yloxy)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0075] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (5.0 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 2-(3-bromopropoxy) tetrahydro-2H-pyran (71 mg, 0.32 mmol). The solution was heated at 120°C for 1 hour, cooled and then water (10 mL) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound (39 mg, 39%) as its acetate salt.

¹H-NMR (data for the acetate salt) : 0.85 (d, 3H), 1.35 (s, 3H), 1.47-1.92 (m, 9H), 2.01-2.10 (m, 4H), 2.38 (m, 1H), 2.56-2.80 (m, 5H), 3.01 (m, 1H), 3.40-3.56 (m, 2H), 3.78-3.90 (m, 2H), 4.58 (m, 1H), 6.64 (d, 1H), 6.79-6.83 (m, 2H), 7.18 (t, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 348.2; C₂₁H₃₃NO₃ + H requires 348.3.

Example 12: (±)-3-[1-(3-Tetrahydro-2H-pyran-2-ylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0076] To a stirred solution of 1-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(tetrahydro-2H-pyran-2-yl)-1-propanone (Preparation 3, 470 mg, 1.36 mmol) in diethyl ether (6.6 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in diethyl ether, 2.72 mL, 2.72 mmol). After 2 hours the reaction was quenched by adding 2N aqueous sodium hydroxide (0.2 mL) followed by water (0.3 mL) and then diethyl ether (15 mL). The solid precipitate was then removed by filtration through a pad of Celite®, washing with ethyl acetate (5 x 50 mL). The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (396 mg, 88%) as a pale yellow oil.

¹H-NMR (selected data) : 0.78 (d, 3H), 1.38 (s, 3H), 1.80 (m, 1H), 1.95 (m, 1H), 2.20-2.70 (m, 5H), 2.78-2.90 (m, 1H), 3.25 (m, 1H), 3.41 (m, 1H), 3.98 (m, 1H), 6.65 (d, 1H), 6.75 (s, 1H), 6.82 (d, 1H), 7.18 (t, 1H).
MS (TSI⁺) : *m/z* [MH⁺] 332.1; C₂₁H₃₃NO₂ + H requires 332.3.

5 Example 13: (±)-3-{1-[3-(1,3-Dioxan-2-yl)propyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0077] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (150 mg, 0.29 mmol) in *N,N*-dimethylformamide (4.0 mL) at room temperature was added sodium hydrogencarbonate (84 mg, 1.00 mmol), and 2-(3-bromopropyl)-1,3-dioxane (Preparation 4, 209 mg, 1.00 mmol). The solution was heated at 100°C for 2 hours, cooled and then added
10 to a mixture of saturated aqueous sodium hydrogencarbonate solution and diethyl ether (100 mL of 1:1). The aqueous layer was extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with water (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by column chromatography on silica gel (10 g), eluting with CH₂Cl₂ : ethanol : 0.88 ammonia (100:8:1), to give the title compound (70 mg, 28%) as a white foam.

¹H-NMR : 0.78 (d, 3H), 1.35-1.70 (m, 9H), 1.90-2.18 (m, 2H), 2.23-2.64 (m, 6H), 2.85 (m, 1H), 3.68-3.79 (m, 2H), 4.02-4.18 (m, 2H), 4.52-4.57 (m, 1H), 6.61 (d, 1H), 6.70-6.80 (m, 2H), 7.15 (t, 1H).

Example 14: (±)-3-[1-(3,3-Dimethoxypropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0078] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 3-chloro-1,1-dimethoxypropane (53 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added sequentially. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined
25 organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (selected data from the acetate salt) : 0.78 (d, 3H), 1.18-1.28 (m, 6H), 1.29 (s, 3H), 3.45-3.70 (m, 4H), 4.60 (t, 1H), 6.62 (dd, 1H), 6.72 (s, 1H), 6.82 (d, 1H), 7.18 (t, 1H).
MS (APCI⁺) : *m/z* [MH⁺] 336.2; C₂₀H₃₃NO₃ + H requires 336.2.

Example 15: (±)-3-{1-[2-(2-Hydroxyethoxy)ethyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0079] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 2-(2-chloroethoxy)-1-ethanol (53 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers
40 were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (data from the acetate salt) : 0.82 (d, 3H), 1.31 (s, 3H), 1.70 (m, 1H), 2.02 (s, 3H), 2.04 (m, 1H), 2.32 (m, 1H), 2.62-2.90 (m, 5H), 3.05 (m, 1H), 3.52-3.80 (m, 6H), 6.66 (dd, 1H), 6.72-6.80 (m, 2H), 7.15 (t, 1H).
MS (APCI⁺) : *m/z* [MH⁺] 294.1; C₁₇H₂₇NO₃ + H requires 294.2.

Example 16: (±)-3-{1-[2-(1,3-Dioxolan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0080] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 2-(2-bromoethyl)-1,3-dioxolane (60 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate,
55 filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (selected data from the acetate salt) : 0.80 (d, 3H), 1.30 (s, 3H), 1.65 (m, 1H), 1.90-1.97 (m, 2H), 2.02 (m,

1H), 2.35 (m, 1H), 2.43-2.70 (m, 5H), 2.90 (m, 1H), 3.80-3.98 (m, 4H), 4.93 (m, 1H), 6.66 (dd, 1H), 6.72-6.82 (m, 2H), 7.15 (t, 1H).

MS (APCI⁺): m/z [MH⁺] 306.3; C₁₈H₂₇NO₃ + H requires 306.2.

5 **Example 17: (±)-3-[1-[4-(1,3-Dioxolan-2-yl)butyl]-*trans*-3,4-dimethylpiperidinyl]phenol**

[0081] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 2-(4-chlorobutyl)-1,3-dioxolane (53 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (selected data from the acetate salt) : 0.81 (d, 3H), 1.38-1.70 (m, 7H), 2.03 (m, 1H), 2.36 (m, 1H), 2.43-2.78 (m, 5H), 2.98 (m, 1H), 3.80-3.98 (m, 4H), 4.93 (m, 1H), 6.66 (dd, 1H), 6.72-6.82 (m, 2H), 7.15 (t, 1H).

MS (APCI⁺): m/z [MH⁺] 334.1; C₂₀H₃₁NO₃ + H requires 334.2.

20 **Example 18: (±)-3-[1-[2-(2,5,5-Trimethyl-1,3-dioxan-2-yl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol**

[0082] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane (76 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (selected data for the free base) : 0.70 (s, 3H), 0.81 (d, 3H), 1.18 (s, 3H), 1.30 (s, 3H), 1.58-1.60 (m, 5H), 3.40 (d, 2H), 3.60 (d, 3H), 6.65 (m, 1H), 6.72-6.82 (m, 2H), 7.15 (t, 1H).

MS (APCI⁺): m/z [MH⁺] 362.1; C₂₂H₃₅NO₃ + H requires 362.3.

35 **Example 19: (±)-3-[1-[2-(Tetrahydro-2H-pyran-2-yloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol**

[0083] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 2-chloroethyl tetrahydro-2H-pyran-2-yl ether (52 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (selected data from the acetate salt) : 0.81 (d, 3H), 1.30 (s, 3H), 1.40-1.92 (m, 7H), 2.01-2.10 (m, 1H), 2.35 (m, 1H), 2.50-2.82 (m, 5H), 2.98 (m, 1H), 3.42-3.62 (m, 2H), 3.82-3.95 (m, 2H), 4.60 (m, 1H), 6.64 (d, 1H), 6.70-6.83 (m, 2H), 7.15 (t, 1H).

MS (APCI⁺): m/z [MH⁺] 334.4; C₂₀H₃₁NO₃ + H requires 334.2.

50 **Example 20: (±)-3-[1-(5-Hydroxypentyl)-*trans*-3,4-dimethylpiperidinyl]phenol**

[0084] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in *N,N*-dimethylformamide (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and 5-chloro-1-pentanol (40 mg, 0.32 mmol) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated at 120°C for 1.5 hours, cooled and then water (30 mL) and ethyl acetate (10 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a Dynamax™ column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of

acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.
¹H-NMR (selected data from the acetate salt) : 0.78 (d, 3H), 1.31 (s, 3H), 1.38-1.70 (m, 7H), 2.84 (m, 1H), 3.65 (t, 2H), 6.61 (d, 1H), 6.75 (s, 1H), 6.83 (d, 1H), 7.15 (t, 1H).
 MS (APCI⁺) : *m/z* [MH⁺] 291.9; C₁₈H₂₉NO₂ + H requires 292.2.

Example 21: (±)-3-[1-(3-Tetrahydro-2H-pyran-4-ylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0085] To a stirred solution of (±)-1-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(tetrahydro-2H-pyran-4-yl)-1-propanone (Preparation 5, 500 mg, 1.45 mmol) in tetrahydrofuran (6 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in diethyl ether, 2.72 mL, 2.72 mmol). After 1 hour, the reaction was quenched first with 2N aqueous sodium hydroxide (0.2 mL) and then water (0.3 mL) and diluted with diethyl ether (25 mL). The solid precipitate was then removed by filtration through a pad of Celite®, washing with ethyl acetate (5 x 50 mL). The filtrate was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound (253 mg, 53%) as a white foam.

¹H-NMR (CD₃OD, selected data for the hydrochloride salt) : 0.82 (d, 3H), 1.45 (s, 3H), 3.90-3.99 (m, 2H), 6.65 (d, 1H), 6.72 (s, 1H), 6.73 (d, 1H), 7.18 (t, 1H).
 MS (TSI⁺) : *m/z* [MH⁺] 331.9; C₂₁H₃₃NO₂ + H requires 332.3.

Example 22: (±)-3-[1-[2-(2-Naphthyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0086] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (82 mg, 0.40 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature was added sodium hydrogencarbonate (35 mg, 0.42 mmol), and 2-(2-iodoethoxy)naphthalene (Preparation 11, 120 mg, 0.40 mmol). The mixture was heated at 150°C for 2 hours, and then at room temperature for 16 hours. The solution was then partitioned between water (5 mL) and diethyl ether (10 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (1 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified using a Waters Sep-Pak™ cartridge packed with silica gel (10 g), eluting with a gradient of CH₂Cl₂ : EtOH : 0.88 ammonia (100:0:0 to 500:20:1), to give the title compound (64 mg, 43%) as a brown solid.

¹H-NMR : 0.82 (d, 3H), 1.38 (s, 3H), 1.62 (m, 1H), 2.02 (m, 1H), 2.37 (m, 1H), 2.50-3.10 (m, 6H), 4.20-4.30 (m, 2H), 6.64 (d, 1H), 6.78 (s, 1H), 6.85 (d, 1H), 7.10-7.22 (m, 3H), 7.36 (t, 1H), 7.45 (t, 1H), 7.70-7.80 (m, 3H).
 MS (TSI⁺) : *m/z* [MH⁺] 376.7; C₂₅H₂₉NO₂ + H requires 376.2.

Example 23: (±)-3-[1-(2-Isopropoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0087] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (82 mg, 0.40 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature was added sodium hydrogencarbonate (35 mg, 0.42 mmol), and 2-(2-iodo-ethoxy)propane (Preparation 13, 86 mg, 0.40 mmol). The mixture was heated at 150°C for 2 hours, and then at room temperature for 16 hours. The reaction mixture was partitioned between water (20 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (1 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified using a Waters Sep-Pak™ cartridge packed with silica gel (10 g), eluting with a gradient of CH₂Cl₂ : EtOH : 0.88 ammonia (100:0:0 to 500:20:1), to give the title compound (59 mg, 51%) as a brown oil.

¹H-NMR : 0.80 (d, 3H), 1.18 (d, 6H), 1.35 (s, 3H), 1.60 (m, 1H), 2.02 (m, 1H), 2.37 (m, 1H), 2.40-2.90 (m, 6H), 3.55-3.65 (m, 3H), 6.64 (d, 1H), 6.78 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H).
 MS (TSI⁺) : *m/z* [MH⁺] 292.3; C₁₈H₂₉NO₂ + H requires 292.2.

Example 24: 3-[1-(2-Propoxyethyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0088] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (82 mg, 0.40 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature was added sodium hydrogencarbonate (35 mg, 0.42 mmol), and 1-(2-iodo-ethoxy)propane (Preparation 15, 86 mg, 0.40 mmol). The mixture was heated at 150°C for 2 hours, and then at room temperature for 16 hours. The reaction mixture was partitioned between water (20 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (1 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified using a Waters Sep-Pak™ cartridge packed with silica gel (10 g), eluting with dichloromethane : ethanol : 0.88 ammonia (500:20:1), to give the title compound (43 mg, 37%) as a brown oil.

¹H-NMR (selected data) : 0.88-0.95 (m, 3H), 0.95 (t, 3H), 1.32 (s, 3H), 3.41 (t, 2H), 3.50-3.64 (m, 2H), 6.66 (d, 1H), 6.78 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H).

MS (APCI⁺) : m/z [MH⁺] 292.0; C₁₈H₂₉NO₂ + H requires 292.2.

Example 25: (±)-3-[1-[2-(Cyclopentyloxy)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0089] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (21 mg, 0.10 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature was added sodium hydrogencarbonate (10 mg, 0.12 mmol), and 1-(2-iodo-ethoxy)cyclopentane (Preparation 17, 15 mg, 0.06 mmol). The mixture was heated at 150°C for 2 hours, and then at room temperature for 16 hours. The reaction mixture was partitioned between water (8 mL) and diethyl ether (15 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (1 x 15 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified using a Waters Sep-PakTM cartridge packed with silica gel (5 g), eluting with a gradient of CH₂Cl₂ : EtOH : 0.88 ammonia (100:0:0 to 500:20:1), to give the title compound (15 mg, 47%) as a brown oil.

¹H-NMR : 0.78 (d, 3H), 1.30 (s, 3H), 1.40-1.80 (m, 9H), 1.98 (m, 1H), 2.35 (m, 1H), 2.42-2.50 (m, 5H), 2.86 (m, 1H), 3.56 (t, 2H), 3.90 (m, 1H), 6.64 (d, 1H), 6.78 (s, 1H), 6.83 (d, 1H), 7.18 (t, 1H).

MS (TSI⁺) : m/z [MH⁺] 318.1; C₂₀H₃₁NO₂ + H requires 318.2.

Example 26: (±)-3-[1-(3-Tetrahydro-2-furanylpropyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0090] To a stirred solution of (±)-1-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(tetrahydro-2-furanyl)-1-propanone (Preparation 6, 270 mg, 0.82 mmol) in tetrahydrofuran (25 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in diethyl ether, 4.0 mL, 4.0 mmol). After 10 minutes at room temperature the reaction was quenched with water. The aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound (170 mg, 67%) as a brown oil.

¹H-NMR : 0.80 (d, 3H), 1.30 (s, 3H), 1.40-2.05 (m, 10H), 2.25-2.70 (m, 6H), 2.85 (m, 1H), 3.65-3.90 (m, 3H), 6.64 (d, 1H), 6.78 (s, 1H), 6.83 (d, 1H), 7.18 (t, 1H).

MS (TSI⁺) : m/z [MH⁺] 318.3; C₂₀H₃₁NO₂ + H requires 318.2.

Example 27: (±)-3-[1-[2-(Cyclohexylsulfanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0091] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (150 mg, 0.29 mmol) in *N,N*-dimethylformamide (10 mL) at room temperature was added sodium hydrogencarbonate (70 mg, 0.80 mmol), sodium iodide (120 mg, 0.80 mmol) and 1-[(2-chloroethyl)sulfanyl]cyclohexane (140 mg, 0.80 mmol). The mixture was heated at reflux for 1 hour, cooled and then water and ethyl acetate were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified by preparative HPLC on a DynamaxTM column, 42 x 250 mm; flow 8.0 mL min⁻¹; employing U.V. detection at 275 nm; eluant gradient of acetonitrile : 0.05 M aqueous ammonium acetate solution (90:10 to 10:90) to afford the title compound as its acetate salt.

¹H-NMR (data for the free base) : 0.79 (d, 3H), 1.20-1.40 (m, 9H), 1.60-2.00 (m, 6H), 2.24-2.95 (m, 10H), 6.60 (d, 1H), 6.70 (s, 1H), 6.80 (d, 1H), 7.12 (t, 1H).

MS (TSI⁺) : m/z [MH⁺] 348.2; C₂₁H₃₃NOS + H requires 348.2.

Example 28: (±)-3-[1-[2-(Ethylsulfanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0092] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (100 mg, 0.49 mmol) in *N,N*-dimethylformamide (2 mL) at room temperature was added sodium hydrogencarbonate (47 mg, 0.56 mmol), sodium iodide (7 mg, 0.05 mmol) and 2-chloroethyl ethyl sulfide (70 µL, 0.56 mmol). The mixture was heated at 140°C for 1 hour, cooled and then concentrated *in vacuo* to give a crude oil. This was purified by column chromatography on silica gel (10 g), eluting with a gradient of dichloromethane : ethanol : 0.88 ammonia (500:8:1 to 300:8:1), to give the title compound (120 mg, 83%) as an orange oil.

¹H-NMR : 0.77 (d, 3H), 1.20 (t, 3H), 1.26 (s, 3H), 1.57 (m, 1H), 1.95 (m, 1H), 2.26 (m, 1H), 2.38 (m, 1H), 2.50-2.68 (m, 8H), 2.81 (m, 1H), 6.59 (d, 1H), 6.71 (s, 1H), 6.81 (d, 1H), 7.12 (t, 1H).

MS (APCI⁺) : m/z [MH⁺] 294.4; C₁₇H₂₇NOS + H requires 294.2.

Example 29: (±)-3-[1-[2-(Ethylsulfinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0093] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (100 mg, 0.49 mmol) in *N,N*-dimethylformamide (2 mL) at room temperature was added sodium hydrogencarbonate (47 mg, 0.56 mmol), sodium iodide (7 mg, 0.05 mmol) and 2-chloroethyl ethyl sulfoxide (Preparation 7, 76 mg, 0.54 mmol). The mixture was heated at reflux for 1.5

hours, cooled and then concentrated *in vacuo* to give a crude oil. This was purified by column chromatography on silica gel (10 g), eluting with dichloromethane : ethanol : 0.88 ammonia (200:8:1), to give the title compound (43 mg, 28%) as a brown solid.

¹H-NMR : 0.70-0.80 (m, 3H), 1.26 (s, 3H), 1.28-1.38 (m, 3H), 1.58 (m, 1H), 1.95 (m, 1H), 2.18-2.90 (m, 11H), 6.61 (d, 1H), 6.71-6.80 (m, 2H), 7.12 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 310.5; C₁₇H₂₇NO₂S + H requires 310.2.

Example 30: (±)-3-{1-[2-(Ethylsulfonyl)ethyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0094] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (100 mg, 0.49 mmol) in *N,N*-dimethylformamide (2 mL) at room temperature was added sodium hydrogencarbonate (47 mg, 0.56 mmol), sodium iodide (7 mg, 0.05 mmol) and 2-chloroethyl ethyl sulfone (Preparation 8, 88 mg, 0.56 mmol). The mixture was heated at 140°C for 1 hour, cooled and then concentrated *in vacuo* to give a crude oil. This was purified by column chromatography on silica gel (10 g), eluting with CH₂Cl₂ : EtOH : 0.88 ammonia (500:8:1), to give the title compound (155 mg, 97%) as an orange oil.

¹H-NMR : 0.70 (m, 3H), 1.27 (s, 3H), 1.35 (t, 3H), 1.59 (m, 1H), 1.96 (m, 1H), 2.22 (m, 1H), 2.38 (m, 1H), 2.47-2.63 (m, 2H), 2.79-2.85 (m, 3H), 2.99-3.18 (m, 4H), 6.61 (d, 1H), 6.72 (s, 1H), 6.80 (d, 1H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 326.4; C₁₇H₂₇NO₃S + H requires 326.2.

Example 31: (±)-3-{1-[3-(1*H*-1,2,3,4-Tetrazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0095] To a solution of (±)-3-[1-(3-hydroxypropyl)-*trans*-3,4-dimethylpiperidinyl]phenol (Example 3, 155 mg, 0.59 mmol), 1*H*-tetrazole (42 mg, 0.60 mmol) and triphenylphosphine (155 mg, 0.59 mmol) in dichloromethane (2 mL) at 0°C was added diethyl azodicarboxylate (103 mg, 0.59 mmol) dropwise *via* syringe. The reaction was stirred at room temperature for 16 hours, and then treated with more triphenylphosphine (75 mg, 0.29 mmol) and diethyl azodicarboxylate (51 mg, 0.29 mmol). After stirring at room temperature for a further 16 hours the reaction was concentrated *in vacuo* to give a crude residue. This was purified by column chromatography on silica gel (20 g), eluting with a gradient of dichloromethane : ethanol : 0.88 ammonia (300:8:1 to 200:8:1), to give the title compound (53 mg, 29%) as an oil.

¹H-NMR : 0.80 (m, 3H), 1.32 (s, 3H), 1.59 (m, 1H), 2.00 (m, 1H), 2.15-2.60 (m, 8H), 2.81 (m, 1H), 4.75 (t, 2H), 6.65 (dd, 1H), 6.76 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H), 8.50 (s, 1H).

MS (APCI⁺) *m/z* [MH⁺] 316.5; C₁₇H₂₅N₅O + H requires 316.2.

Example 32: (±)-3-{1-[3-(1*H*-Pyrazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0096] To a stirred solution of (±)-1-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(1*H*-pyrazol-1-yl)-1-propanone (Preparation 9, 71 mg, 0.22 mmol) in tetrahydrofuran (3 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in diethyl ether, 0.4 mL, 0.4 mmol). After 10 minutes at room temperature the reaction was quenched with water and diluted with ethyl acetate. The solid precipitate was removed by filtration through a pad of Celite®, and brine was added to the filtrate. The two layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound (49 mg, 71 %) as an oil.

¹H-NMR (CD₃OD, selected data) : 0.80 (d, 3H), 1.38 (s, 3H), 6.32 (s, 1H), 6.61 (d, 1H), 6.68 (s, 1H), 6.72 (d, 1H), 7.15 (t, 1H), 7.58 (s, 1H), 7.70 (s, 1H).

MS (TSI⁺) : *m/z* [MH⁺] 314.3; C₁₉H₂₇N₃O + H requires 314.2.

Example 33: (±)-3-{1-[3-(4-Pyridinyl)propyl]-*trans*-3,4-dimethylpiperidinyl}phenol

[0097] To a solution of 4-pyridinepropanol (1.0 g, 7.29 mmol) in dichloromethane (25 mL) at 0°C was added methanesulfonyl chloride (0.90 g, 7.90 mmol). The mixture was stirred at room temperature for 1 hour and was then concentrated *in vacuo*. This crude oil was dissolved in 1,2-dimethoxyethane (10 mL) and then added to a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (300 mg, 1.46 mmol) and sodium hydrogencarbonate (1.0 g, 11.9 mmol). The mixture was heated at reflux for 16 hours, cooled and then filtered. The filtrate was concentrated *in vacuo* to give a crude residue which was purified by column chromatography on silica gel, eluting with a gradient of dichloromethane : methanol (98:2 to 0:100). This gave the title compound as a pale brown solid.

¹H-NMR (D₂O, selected data for the HCl salt) : 0.70 (d, 3H), 1.30 (s, 3H), 6.70 (d, 1H), 6.78 (s, 1H), 6.88 (d, 1H), 7.20 (t, 1H), 7.22-7.25 (m, 2H), 8.29-8.35 (m, 2H).

MS (TSI⁺) : *m/z* [MH⁺] 325.5; C₂₁H₂₈N₂O + H requires 325.2.

Example 34: (±)-3-[1-[3-(1*H*-1,2,4-Triazol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0098] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (150 mg, 0.73 mmol) in *N,N*-dimethylformamide (6 mL) at room temperature was added sodium hydrogencarbonate (62 mg, 0.80 mmol), and 1-(3-bromopropyl)-1*H*-1,2,4-triazole (prepared as described in DE 4115433 A1: 152 mg, 0.80 mmol). The mixture was heated at reflux for 1.5 hours, and then at room temperature for 16 hours. The solution was then poured into water (100 mL) and made basic (pH 9) with 2*N* aqueous sodium hydroxide solution. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a crude oil. This was purified using a Waters Sep-Pak™ cartridge packed with silica gel (10 g), eluting with dichloromethane : ethanol : 0.88 ammonia (200:8:1), to give the title compound (130 mg, 57%) as a yellow oil.

¹H-NMR: 0.80 (m, 3H), 1.30 (s, 3H), 1.59 (m, 1H), 1.95-2.38 (m, 7H), 2.48-2.58 (m, 2H), 2.78 (m, 1H), 4.26 (t, 2H), 6.62 (m, 1H), 6.78 (m, 1H), 6.84 (d, 1H), 7.15 (t, 1H), 7.95 (s, 1H), 8.05 (s, 1H).

MS (TSI⁺): *m/z* [MH⁺] 315.6; C₁₈H₂₆N₄O + H requires 315.2.

Example 35: (±)-3-[1-[3-(1*H*-Pyrrol-1-yl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0099] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), and 1-(3-bromopropyl)-1*H*-pyrrole (43 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR (selected data): 0.81 (d, 3H), 1.28 (s, 3H), 3.98 (t, 3H), 6.05-6.15 (m, 2H), 6.60-6.69 (m, 3H), 6.78 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H).

MS (APCI⁺): *m/z* [MH⁺] 313.1; C₂₀H₂₈N₂O + H requires 313.2.

Example 36: (±)-3-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidinyl]-1-(4-morpholinyl)-1-propanone

[0100] To a solution of 4-acryloylmorpholine (152 mg, 1.08 mmol) in tetrahydrofuran (4 mL) at room temperature was added (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (200 mg, 0.97 mmol). The mixture was heated at reflux for 16 hours and then cooled. The solvent was removed *in vacuo* to give a pale yellow oil. This was purified by column chromatography, eluting with a gradient of CH₂Cl₂ : EtOH : 0.88 ammonia (300:8:1 to 100:8:1), to give the title compound (327 mg, 97%) as a white solid.

¹H-NMR: 0.72 (d, 3H), 1.27 (s, 3H), 1.58 (m, 1H), 1.95 (m, 1H), 2.20-2.85 (m, 9H), 3.42-3.48 (m, 2H), 3.52-3.62 (m, 6H), 6.60 (m, 1H), 6.73 (s, 1H), 6.79 (d, 1H), 7.12 (t, 1H).

MS (TSI⁺): *m/z* [MH⁺] 347.4; C₂₀H₃₀N₂O₃ + H requires 347.2.

Example 37: 3-[1-[3-(4-Morpholinyl)propyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0101] To a stirred solution of (±)-3-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]-1-(4-morpholinyl)-1-propanone (Example 36, 150 mg, 0.43 mmol) in tetrahydrofuran (3 mL) at 0°C was added lithium aluminium hydride (1.0 M solution in diethyl ether, 0.47 mL, 0.47 mmol). After 15 minutes at 0°C the mixture was warmed to room temperature and stirred at ambient temperature for 16 hours. The reaction was quenched with a saturated ammonium chloride solution (5 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography on silica gel (7.5 g), eluting with dichloromethane : ethanol : 0.88 ammonia (100:8:1), to give the title compound (124 mg, 87%) as a pale yellow oil.

¹H-NMR: 0.75 (d, 3H), 1.26 (s, 3H), 1.57 (m, 1H), 1.62-1.70 (m, 2H), 1.98 (m, 1H), 2.25-2.59 (m, 12H), 2.80 (m, 1H), 3.67-3.71 (m, 4H), 6.59 (m, 1H), 6.72 (s, 1H), 6.78 (d, 1H), 7.12 (t, 1H).

MS (APCI⁺): *m/z* [MH⁺] 333.1; C₂₀H₃₂N₂O₂ + H requires 333.3.

Example 38: 3-[1-[2-(1-Azepanyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0102] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and a mixture of 1-(2-chloroethyl)azepane hydrochloride (64 mg, 0.32 mmol) and triethylamine (32 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR : 0.78 (d, 3H), 1.28 (s, 3H), 1.56-1.78 (m, 9H), 1.97 (m, 1H), 2.20-2.43 (m, 2H), 2.56-2.98 (m, 11H), 6.67 (m, 1H), 6.72-6.81 (m, 2H), 7.15 (t, 1H).
MS (APCI⁺) : *m/z* [MH⁺] 331.1; C₂₁H₃₄N₂O + H requires 331.3.

Example 39: 3-[1-[2-(4-Morpholinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0103] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and a mixture of 4-(2-chloroethyl)morpholine hydrochloride (60 mg, 0.32 mmol) and triethylamine (32 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR : 0.82 (d, 3H), 1.35 (s, 3H), 1.72 (m, 1H), 2.10 (m, 1H), 2.33-2.86 (m, 12H), 2.98 (m, 1H), 3.68-3.77 (m, 4H), 6.67 (m, 1H), 6.78 (s, 1H), 6.84 (d, 1H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 319.2; C₁₉H₃₀N₂O₂ + H requires 319.2.

Example 40: 3-[1-[2-(1-Piperidinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0104] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and a mixture of 1-(2-chloroethyl)piperidine hydrochloride (59 mg, 0.32 mmol) and triethylamine (32 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR : 0.79 (d, 3H), 1.29 (s, 3H), 1.40-1.80 (m, 7H), 2.01 (m, 1H), 2.20-2.90 (m, 13H), 6.65 (m, 1H), 6.75 (s, 1H), 6.80 (d, 1H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 317.1; C₂₀H₃₂N₂O + H requires 317.3.

Example 41: 3-[1-[2-(1-Pyrrolidinyl)ethyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0105] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and a mixture of 1-(2-chloroethyl)pyrrolidine hydrochloride (54 mg, 0.32 mmol) and triethylamine (32 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR : 0.79 (d, 3H), 1.29 (s, 3H), 1.58 (m, 1H), 1.67-1.90 (m, 4H), 2.01 (m, 1H), 2.20-2.90 (m, 13H), 6.65 (m, 1H), 6.70 (s, 1H), 6.81 (d, 1H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 303.1; C₁₉H₃₀N₂O + H requires 303.2.

Example 42: 3-[1-[3-(1-Piperidinyl)propyl]-*trans*-3,4-dimethyl piperidinyl]phenol

[0106] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (60 mg, 0.29 mmol) in acetonitrile (2.5 mL) at room temperature was added sodium hydrogencarbonate (27 mg, 0.32 mmol), sodium iodide (48 mg, 0.32 mmol) and a mixture of 1-(3-chloropropyl)piperidine hydrochloride (63 mg, 0.32 mmol) and triethylamine (32 mg, 0.32 mmol) in acetonitrile (2.5 mL). The solution was heated at reflux for 3 hours, cooled and then water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as an oil.

¹H-NMR : 0.80 (d, 3H), 1.25-2.01 (m, 13H), 2.20-2.95 (m, 13H), 6.65 (m, 1H), 6.72-6.81 (m, 2H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 331.2; C₂₁H₃₄N₂O + H requires 331.3.

Example 43: (±)-3-[1-(3-Methoxyphenyl)-*trans*-3,4-dimethylpiperidinyl]phenol

[0107] To a solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (82 mg, 0.40 mmol), 3-bromoanisole (56 µL, 0.44 mmol) and tri-*o*-tolylphosphine (5 mg, 0.04 mmol) in toluene (2 mL) was added sodium *tert*-butoxide (54 mg, 0.56 mmol) and tris(dibenzylideneacetone)-palladium(0) (8 mg, 0.02 mmol) and the reaction mixture was heated at reflux for 6 h. After cooling, the reaction mixture was concentrated *in vacuo* to give the crude product which was purified by column chromatography on silica gel, eluting with a gradient of methanol : dichloromethane : 0.880 ammonia (10:990:

1 to 30:970:3), to give the title compound (36 mg, 29%) as a yellow oil.

¹H-NMR (C₆D₆) : 0.78 (d, 3H), 1.08 (s, 3H), 1.25 (m, 1H), 1.72 (m, 1H), 2.10 (m, 1H), 2.70 (m, 1H), 2.95 (m, 1H), 3.15 (m, 1H), 3.32 (m, 1H), 3.39 (s, 3H), 4.01 (br s, 1H), 6.34-6.40 (m, 2H), 6.52-6.55 (m, 2H), 6.64 (m, 1H), 6.67 (m, 1H), 7.01 (t, 1H), 7.15 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 312.1; C₂₀H₂₅NO₂ + H requires 312.2.

Example 44: (±)-3-[1-[4-(Dimethylamino)phenyl]-*trans*-3,4-dimethylpiperidinyl]phenol

[0108] To a stirred solution of (±)-4-(3-hydroxyphenyl)-*trans*-3,4-dimethylpiperidine (82 mg, 0.40 mmol), *N,N*-dimethyl-4-bromoaniline (112 mg, 0.56 mmol) and tri-*o*-tolylphosphine (5 mg, 0.04 mmol) in toluene (2 mL) was added sodium *tert*-butoxide (54 mg, 0.56 mmol) and tris(dibenzylideneacetone)palladium(0) (8 mg, 0.02 mmol) and the reaction mixture was heated at reflux for 48 hours. After cooling, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product. This was purified by column chromatography on silica gel, eluting with a gradient of methanol : dichloromethane : 0.88 ammonia (10:990:1 to 20:980:1), to give the title compound (23 mg, 18%) as a yellow oil.

¹H-NMR (C₆D₆) : 0.91 (d, 3H), 1.16 (s, 3H), 1.32 (m, 1H), 1.74 (m, 1H), 2.12 (m, 1H), 2.44-2.58 (m, 6H), 2.75 (m, 1H), 3.03 (m, 2H), 3.21 (m, 1H), 6.57 (m, 1H), 6.69 (m, 1H), 6.71-6.76 (m, 3H), 6.83-6.92 (m, 2H), 7.07 (t, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 325.2; C₂₁H₂₈N₂O + H requires 325.2.

Example 45 : (±)-Methyl 3-[*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidinyl]propionate

[0109] To a stirred solution of (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (82 mg, 0.40 mmol) in methanol (3 mL) at room temperature was added methyl acrylate (54 μL, 0.6 mmol). After 2 hours at room temperature the reaction mixture was concentrated *in vacuo* to give the crude product. This was purified by column chromatography on silica gel, eluting with a gradient of methanol : dichloromethane : 0.880 ammonia (10:990:1 to 30:970:3), to give the title compound (60 mg, 51 %) as a pale yellow oil.

¹H-NMR (C₆D₆, data for the free base) : 0.82 (d, 3H), 1.13 (s, 3H), 1.32 (m, 1H), 1.73 (m, 1H), 2.09 (m, 1H), 2.17-2.35 (m, 5H), 2.46-2.59 (m, 3H), 3.29 (s, 3H), 5.90 (br s, 1H), 6.63 (dd, 1H), 6.69 (d, 1H), 6.76 (m, 1H), 7.06 (m, 1H).

MS (APCI⁺) : *m/z* [MH⁺] 292.3; C₁₇H₂₅NO₃ + H requires 292.2.

Example 46

[0110] Compounds according to the present invention, for example the compound of Example 5, were found to display anti-pruritic activity when tested in accordance with the above procedure.

Preparation of Starting Materials

Preparation 1: 3-(Tetrahydro-3-furanyl)propionic acid

[0111] To a solution of *trans*-3-furanacrylic acid (10 g, 72.4 mmol) in industrial methylated spirits (50 mL) was added 10% palladium on carbon (1.0 g) at room temperature. The reaction vessel was charged with hydrogen gas to a pressure of 345 kPa and stirred at room temperature for 16 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the title compound as a colourless oil.

¹H-NMR : 1.44-1.58 (m, 1H), 1.61-1.82 (m, 2H), 1.99-2.12 (m, 1H), 2.15-2.48 (m, 3H), 3.38 (t, 1H), 3.62-3.98 (m, 3H).

Preparation 2: (±)-1-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(tetrahydro-3-furanyl)-1-propanone

[0112] To a solution of 3-(tetrahydro-3-furanyl)propionic acid (Preparation 1, 202 mg, 1.40 mmol) in *N,N*-dimethylformamide (40 mL) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (320 mg, 1.70 mmol) and 1-hydroxybenzotriazole (204 mg, 1.51 mmol). After the mixture had become homogeneous, (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (300 mg, 1.46 mmol) was added in one portion. The mixture was stirred at room temperature for 16 hours and then water was added. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude clear residue. This was purified by column chromatography on silica gel, eluting with ethyl acetate, to give the title compound (150 mg, 30%) as a colourless oil.

¹H-NMR (5:4 mixture of rotamers) : 0.56-0.61 (m, 3H), 1.28-1.35 (m, 3H), 1.40-1.76 (m, 4H), 1.95-2.45 (m, 6H), 2.85 (m, 0.56H), 3.10 (m, 0.44H), 3.28-3.90 (m, 6H), 4.30 (m, 0.44H), 4.61 (m, 0.56H), 6.60-6.77 (m, 3H), 7.10 (m, 1H).

Preparation 3: (±)-1-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidiny]-3-(tetrahydro-2H-pyran-2-yl)-1-propanone

[0113] To a solution of 3-(tetrahydropyran-2-yl)propionic acid (prepared as described in *Chem. Ber.*, 1990, 123, 153: 243 mg, 1.54 mmol) in *N,N*-dimethylformamide (55 mL) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (420 mg, 2.19 mmol) and 1-hydroxybenzotriazole (223 mg, 1.65 mmol). After the mixture had become homogeneous, (±)-3-(*trans*-3,4-dimethylpiperidiny)phenol (338 mg, 1.65 mmol) was added in one portion. The mixture was stirred at room temperature for 48 hours and then water (50 mL) was added. The aqueous layer was extracted with diethyl ether (2 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give a clear residue. This was purified by column chromatography on silica gel, eluting with a gradient of ethyl acetate : hexane (66:44 to 75:25), to give the title compound (473 mg, 90%) as a colourless oil.

¹H-NMR (selected data from mixture of rotamers (approximately 1:1)) : 0.59-0.68 (m, 3H), 1.38-1.41 (m, 3H), 2.87 (m, 0.5H), 3.15 (m, 0.5H), 3.50-3.70 (m, 1H), 4.35 (m, 0.5H), 4.70 (m, 0.5H), 6.68 (d, 1H), 6.72-6.80 (m, 2H), 7.18 (t, 1H). MS (ESI⁺) : *m/z* [MH⁺] 346.3; C₂₁H₃₁NO₃ + H requires 346.2.

Preparation 4: 2-(3-Bromopropyl)-1,3-dioxane

[0114] To a solution of 4-bromobutanal (prepared as described in *J. Org. Chem.*, 1979, 44, 3230-3238: 450 mg, 2.98 mmol) in tetrahydrofuran (10 mL) at room temperature was added 1,3-propane diol (1.0 mL, 13.7 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol). The mixture was heated at reflux for 2 hours, cooled and suspended in a mixture of water and diethyl ether (200 mL of 1:1). The two layers were separated and the organic layer was dried over magnesium sulfate, filtered, and then concentrated *in vacuo* to give the title compound as a clear oil.

¹H-NMR : 1.25-2.20 (m, 6H), 3.43 (t, 2H), 3.75 (m, 2H), 4.10 (dd, 2H), 4.58 (t, 1H).

Preparation 5: (±)-1-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidiny]-3-(tetrahydro-2H-pyran-4-yl)-1-propanone

[0115] To a solution of 3-(tetrahydropyran-4-yl)propionic acid (prepared as described in *Justus Leibigs Ann. Chem.*, 1937, 532, 83: 320 mg, 2.02 mmol) in *N,N*-dimethylformamide (70 mL) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (552 mg, 2.88 mmol) and 1-hydroxybenzotriazole (293 mg, 2.17 mmol). After the mixture had become homogeneous, (±)-3-(*trans*-3,4-dimethylpiperidiny)phenol (338 mg, 1.65 mmol) was added in one portion. The mixture was stirred at room temperature for 16 hours and then water (50 mL) was added. The aqueous layer was extracted with diethyl ether (2 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give a clear residue. This was purified by column chromatography on silica gel (25 g), eluting with a gradient of ethyl acetate : hexane (66:44 to 75:25), to give the title compound (500 mg, 72%) as a colourless oil.

¹H-NMR (selected data from a 4:3 mixture of rotamers) : 0.60-0.68 (m, 3H), 1.38-1.40 (m, 3H), 4.38 (m, 0.43H), 4.70 (m, 0.57H), 6.68 (d, 1H), 6.72-6.80 (m, 2H), 7.18 (t, 1H).

MS (ESI⁺) : *m/z* [MH⁺] 346.1; C₂₁H₃₁NO₃ + H requires 346.2.

Preparation 6: (±)-1-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidiny]-3-(tetrahydro-2-furanyl)-1-propanone

[0116] To a solution of 3-(tetrahydro-2-furanyl)propionic acid (prepared as described in *J. Amer. Chem. Soc.*, 1923, 45, 3042 : 202 mg, 1.40 mmol), in *N,N*-dimethylformamide (50 mL) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (320 mg, 2.00 mmol) and 1-hydroxybenzotriazole (204 mg, 1.50 mmol). After the mixture become homogeneous, (±)-3-(*trans*-3,4-dimethylpiperidiny)phenol (300 mg, 1.50 mmol) was added in one portion. The mixture was stirred at room temperature for 16 hours and then water was added. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a clear residue. This was purified by column chromatography on silica gel, eluting with a gradient of ethyl acetate : dichloromethane (0:100 to 100:0), to give the title compound (270 mg, 58%) as a colourless gum.

¹H-NMR (4:3 mixture of rotamers) : 0.58-0.63 (m, 3H), 1.35-1.38 (m, 3H), 1.40-2.60 (m, 11H), 2.82-3.90 (m, 6H), 4.35 (m, 0.43H), 4.68 (m, 0.57H), 6.64 (d, 1H), 6.72-6.78 (m, 2H), 7.15 (t, 1H).

Preparation 7: 2-Chloroethyl ethyl sulfoxide

[0117] To a solution of 3-chloroperoxybenzoic acid (2.95 g, 8.55 mmol) in dichloromethane (25 mL) at 0°C was added

2-chloroethyl ethyl sulfide (1.0 mL, 8.58 mmol). After 10 minutes at 0°C the cooling bath was removed and the mixture was stirred at room temperature for 48 hours. The reaction mixture was diluted with dichloromethane (75 mL) and then poured into a saturated aqueous sodium hydrogencarbonate solution (100 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil. This was purified by column chromatography on silica gel (50 g), eluting with ethyl acetate, to give the title compound (740 mg, 61 %) as a yellow oil.

¹H-NMR: 1.33 (t, 3 H), 2.70-2.81 (m, 2H), 2.92-3.05 (m, 2H), 3.85-3.96 (m, 2H).

MS (TSI⁺): *m/z* [MNH₄⁺] 157.9; C₄H₉ClOS + NH₄ requires 158.0.

Preparation 8: 2-Chloroethyl ethyl sulfone

[0118] To a solution of 2-chloroethyl ethyl sulfide (1.1 g, 8.58 mmol) in dichloromethane (25 mL) at room temperature was added 3-chloroperoxybenzoic acid (5.9 g, 17.0 mmol) portionwise. The reaction was exothermic and needed to be cooled in an ice bath to complete the addition. A thick white suspension formed and more dichloromethane (25 mL) was added. The mixture was stirred at room temperature for 16 hours and then filtered washing with dichloromethane. The filtrate was washed with a saturated aqueous sodium hydrogencarbonate solution (200 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a colourless oil. This was purified by column chromatography on silica gel (50 g), eluting with ethyl acetate : hexane (1:3), to give the title compound (1.2 g, 90%) as a colourless oil.

¹H-NMR: 1.40 (t, 3 H), 3.08 (q, 2H), 3.35 (t, 2H), 3.90 (t, 2H).

MS (TSI⁺): *m/z* [MNH₄⁺] 173.8; C₄H₉ClO₂S + NH₄ requires 174.0.

Preparation 9: (±)-1-[*trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidinyl]-3-(1*H*-pyrazol-1-yl)-1-propanone

[0119] To a solution of 3-(pyrazol-1-yl)propionic acid (prepared as described in *Synlett*, 1997, 1013-1034: 225 mg, 1.60 mmol), in *N,N*-dimethylformamide (50 mL) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (418 mg, 2.18 mmol) and 1-hydroxybenzotriazole (216 mg, 1.60 mmol). After 15 minutes at room temperature the solution was homogeneous and (±)-3-(*trans*-3,4-dimethylpiperidinyl)phenol (293 mg, 1.43 mmol) was added portionwise. The mixture was stirred at room temperature for 16 hours and then poured into water. The aqueous layer was extracted with diethyl ether (1 x 20 mL), and then made basic with a 2*N* aqueous sodium hydroxide solution (to pH 10), and further extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound (71 mg, 14%) as an oil. This was used in the next step without further purification.

MS (APCI⁺): *m/z* [MH⁺] 328.0; C₁₉H₂₅N₃O₂ + H requires 328.2.

Preparation 10: 2-(2-Naphthyloxy)ethyl 4-bromobenzenesulfonate

[0120] To a solution of 2-(2-naphthyloxy)-1-ethanol (1.5 g, 7.97 mmol) and triethylamine (1.21 g, 11.95 mmol) in dichloromethane (20 mL) at 0°C was added 4-bromobenzenesulfonyl chloride (2.12 g, 8.36 mmol) in dichloromethane (10 mL) dropwise over 30 minutes. The reaction was then warmed to room temperature and stirred for 16 hours before more 4-bromobenzenesulfonyl chloride (0.20 g, 0.80 mmol) was added and stirring was continued for 2 hours. The mixture was then poured into water (50 mL) and acidified with 2*N* aqueous hydrochloric acid (15 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude residue. This was purified by column chromatography on silica gel (50 g), eluting with hexane : ethyl acetate (9:2), to give the title compound (0.56 g, 17%) as a white crystalline solid.

¹H-NMR: 4.25-4.31 (m, 2H), 4.45-4.55 (m, 2H), 6.92-7.02 (m, 2H), 7.36 (t, 1H), 7.45 (t, 1H), 7.62-7.85 (m, 7H).

MS (TSI⁺): *m/z* [MNH₄⁺] 424.0; C₁₈H₁₅BrO₄S + NH₄ requires 424.0.

Preparation 11: 2-(2-Iodoethoxy)naphthalene

[0121] To a solution of 2-(2-naphthyloxy)ethyl 4-bromobenzenesulfonate (Preparation 10, 380 mg, 0.93 mmol) in acetone (5 mL) at room temperature was added sodium iodide (1.0 g, 6.66 mmol). The mixture was heated at 35°C for 16 hours and then cooled. The residual precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between diethyl ether (20 mL) and water (20 mL). The two layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (200 mg, 72%) as a pale yellow oil.

¹H-NMR: 3.50 (t, 2H), 4.39 (t, 2H), 7.10-7.20 (m, 2H), 7.30-7.50 (m, 2H), 7.65-7.84 (m, 3H).

Preparation 12: 2-Isopropoxyethyl 4-bromobenzenesulfonate

[0122] To a solution of 2-isopropoxy-1-ethanol (1.5 g, 14.4 mmol) and triethylamine (2.2 g, 21.6 mmol) in dichloromethane (20 mL) at 0°C was added 4-bromobenzenesulfonyl chloride (2.12 g, 8.36 mmol) in dichloromethane (10 mL) dropwise over 30 minutes. The reaction was then warmed to room temperature and stirred for 16 hours. The mixture was then poured into water (50 mL) and acidified with 2N aqueous hydrochloric acid (15 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude residue. This was purified by column chromatography on silica gel (50 g), eluting with hexane : ethyl acetate (9:3), to give the title compound (4.0 g, 86%) as a colourless oil.

¹H-NMR : 1.08 (d, 6H), 3.52 (m, 1H), 3.60 (t, 2H), 4.19 (t, 2H), 7.70 (d, 2H), 7.80 (d, 2H).

Preparation 13: 2-(2-Iodoethoxy)propane

[0123] To a solution of 2-isopropoxyethyl 4-bromobenzenesulfonate (Preparation 12, 1.0 g, 3.08 mmol) in acetone (5 mL) at room temperature was added sodium iodide (1.0 g, 6.66 mmol). The mixture was heated at 35°C for 16 hours and then cooled. The residual precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between diethyl ether (20 mL) and water (20 mL). The two layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (180 mg, 27%) as a pale brown oil.

¹H-NMR : 1.19 (d, 6H), 3.22 (t, 2H), 3.60-3.72 (m, 3H).

Preparation 14: 2-Propoxyethyl 4-bromobenzenesulfonate

[0124] To a solution of 2-propoxy-1-ethanol (1.5 g, 14.4 mmol) and triethylamine (2.2 g, 21.6 mmol) in dichloromethane (20 mL) at 0°C was added 4-bromobenzenesulfonyl chloride (3.86 g, 15.1 mmol) in dichloromethane (10 mL) dropwise over 30 minutes. The reaction was then warmed to room temperature and stirred for 16 hours. The mixture was then poured into water (50 mL) and acidified with 2N aqueous hydrochloric acid (15 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude residue. This was purified by column chromatography on silica gel (50 g), eluting with hexane : ethyl acetate (9:3), to give the title compound (2.2 g, 48%) as a colourless oil.

¹H-NMR : 0.86 (t, 3H), 1.52 (m, 2H), 3.36 (t, 2H), 3.62 (t, 2H), 4.21 (t, 2H), 7.70 (d, 2H), 7.80 (d, 2H).

MS (ESI⁺) : *m/z* [MNH₄⁺] 323.0; C₁₁H₁₅BrO₄S + H requires 323.0.

Preparation 15: 1-(2-Iodoethoxy)propane

[0125] To a solution of 2-propoxyethyl 4-bromobenzenesulfonate (Preparation 14, 1.0 g, 3.08 mmol) in acetone (5 mL) at room temperature was added sodium iodide (1.0 g, 6.66 mmol). The mixture was heated at 35°C for 16 hours and then cooled. The residual precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between diethyl ether (20 mL) and water (20 mL). The two layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (400 mg, 61 %) as a pale yellow oil.

¹H-NMR : 0.92 (t, 3H), 1.60 (m, 2H), 3.24 (t, 2H), 3.42 (t, 2H), 3.70 (t, 2H).

Preparation 16: 2-(Cyclopentyloxy)ethyl 4-bromobenzenesulfonate

[0126] To a solution of 2-(cyclopentyloxy)-1-ethanol (prepared as described in *J. Org. Chem.*, 1968, **33**, 2271-2284 : 127 mg, 0.97 mmol) and triethylamine (101 mg, 0.1 mmol) in dichloromethane (3 mL) at 0°C was added 4-bromobenzenesulfonyl chloride (255 mg, 0.1 mmol) in dichloromethane (2 mL) dropwise over 5 minutes. The reaction was then warmed to room temperature and stirred for 16 hours. The mixture was then poured into water (3 mL) and the two layers were separated. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude residue. This was purified by column chromatography on silica gel (50 g), eluting with a gradient of dichloromethane : hexane (50:50 to 0:100), to give the title compound (200 mg, 59%) as a colourless oil.

¹H-NMR : 1.40-1.78 (m, 8H), 3.57 (t, 2H), 3.80-3.90 (m, 1H), 4.20 (t, 2H), 7.67 (d, 2H), 7.78 (d, 2H).

MS (ESI⁺) : *m/z* [MNH₄⁺] 366.0; C₁₃H₂₁BrO₄S + NH₄ requires 366.0.

Preparation 17: 1-(2-Iodoethoxy)cyclopentane

[0127] To a solution of 2-(cyclopentyloxy)ethyl 4-bromobenzenesulfonate (Preparation 16, 60 mg, 0.17 mmol) in

acetone (5 mL) at room temperature was added sodium iodide (200 mg, 1.3 mmol). The mixture was heated at 35°C for 16 hours and then cooled. The residual precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between diethyl ether (10 mL) and water (10 mL). The two layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (15 mg, 37%) as a brown oil.

¹H-NMR : 1.42-1.80 (m, 8H), 3.22 (t, 2H), 3.67 (t, 2H), 3.93-4.01 (m, 1H).

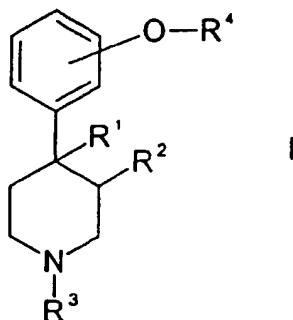
Preparation 18: 2-(Cyclohexyloxy)ethyl-4-methylbenzenesulfonate

[0128] To a solution of 2-(cyclohexyloxy)-1-ethanol (200 mg, 1.39 mmol) in pyridine (10 mL) at 0°C was added p-toluenesulfonyl chloride (292 mg, 1.53 mmol) portionwise followed by 4-(dimethylamino)pyridine (a few crystals) and the mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* to give a crude residue that was partitioned between dichloromethane and 2N aqueous hydrochloric acid. The two layers were separated and the organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography on silica gel, eluting with dichloromethane, to give the title compound (226 mg, 54%) as a yellow oil.

MS (ESI⁺) : *m/z* [MH⁺] 299.3; C₁₅H₂₂SO₄ + H requires 299.1.

Claims

1. A compound of formula I,



wherein

R¹ and R² are each independently H or C₁₋₄ alkyl;

R³ represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and -N(R^{5a})(R^{5b})), C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl or C₃₋₁₀ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, CN, halo, C₁₋₆ alkoxy carbonyl, C₂₋₆ alkanoyl, C₂₋₆ alkanoyloxy, C₃₋₈ cycloalkyl, C₄₋₉ cycloalkanoyl, N(R^{6a})S(O)₂R⁷, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A¹-N(R^{6b})(R^{6c});
n is 0, 1 or 2;

W represents a single bond, C(O) or S(O)_p;

A¹ represents a single bond or C₁₋₁₀ alkylene;

provided that when both W and A¹ represent single bonds, then the group -N(R^{6b})(R^{6c}) is not directly attached to an unsaturated carbon atom; p is 0, 1 or 2;

R^{5a} to R^{5d} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkyl-phenyl, aryl (which latter six groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het²;

provided that R^{5d} does not represent H when n represents 1 or 2;

R^{6a} to R^{6c} each independently represent H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₁₋₄ alkyl-phenyl, aryl (which latter six groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het³, or R^{6b} and R^{6c} together represent unbranched C₂₋₆ alkylene which alkylene group is optionally interrupted by O, S and/or an N(R⁸) group and is optionally substituted by one or more C₁₋₄ alkyl groups;

R⁷ represents C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkylphenyl or aryl, which four groups are optionally substituted by one or more substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, OH, nitro, amino or halo;

R⁸ represents H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, A²-(C₃₋₈ cycloalkyl) or A²-aryl;

A² represents C₁₋₆, alkylene;

Het¹, Het² and Het³ independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms); and

R⁴ represents H, C₁₋₅ alkyl, C₁₋₁₂ alkanoyl, (pyridin-3-yl)carbonyl or (pyridin-4-yl)carbonyl (which latter two groups are optionally in the pyridine N-oxide form);

or a pharmaceutically, or a veterinarily, acceptable derivative thereof;

provided that, when the group OR⁴ is attached to the benzene ring at the *meta*-position relative to the piperidine ring and the piperidine is not in the *N*-oxide form, then:

(a) when R¹ and R² both represent C₁₋₄ alkyl, then R³ does not represent:- C₁₋₈ alkyl (optionally terminally substituted by C₄₋₈ cycloalkyl);

unsubstituted C₃₋₈ alkenyl;

unsubstituted C₃₋₈ alkynyl;

C₁₋₃ alkyl, terminally substituted by phenyl, phenoxy, -S-phenyl, -N(H)-phenyl or -N(C₁₋₄ alkyl)-phenyl, furan-2-yl or thiophen-2-yl; C₁₋₄ alkyl, terminally substituted by an OH group and a further group selected from phenyl, furan-2-yl and thiophen-2-yl; or

C₃₋₅ alkenyl, terminally substituted by phenyl, furan-2-yl or thiophen-2-yl, where the position of unsaturation is at the carbon atoms that are α, β to the phenyl, furan-2-yl or thiophen-2-yl group;

all of which phenyl, phenoxy and phenylthio groups are optionally substituted by one or two substituents selected from OH, C₁₋₃ alkyl, C₁₋₃ alkoxy, halo, nitro, amino and CF₃; and

all of which furanyl and thiophenyl groups are optionally substituted by a methyl group; and

(b) when R¹ represents methyl, and:-

(i) R² represents C₁₋₄ alkyl and R⁴ represents H or C₁₋₄ alkanoyl, then R³ does not represent:-

unsubstituted C₃₋₈ alkyl;

unsubstituted C₄₋₈ alkenyl;

C₃₋₆ alkyl, substituted by an unsubstituted C₄₋₈ cycloalkyl group; C₂ alkyl, terminally substituted by an unsubstituted C₅₋₉ cycloalkanoyl, an unsubstituted C₂₋₆ alkanoyl group or an unsubstituted thiophenyl group;

C₄₋₉ alkyl (optionally substituted at 4- to 9-C position by C₄₋₈ cycloalkyl) or C₅₋₉ alkenyl, which alkyl or alkenyl groups are substituted at the 3-C position by OH, C₁₋₆ alkoxy, oxy-C₁₋₃-alkylphenyl or C₂₋₅ alkanoyloxy (which latter three groups are all unsubstituted); or

C₃ alkyl, terminally substituted by (1) OH, C₁₋₆ alkoxy, oxy-C₁₋₃-alkylphenyl or C₂₋₅ alkanoyloxy (which latter three groups are all unsubstituted) and (2) C₄₋₈ cycloalkyl, thiophenyl (which latter two groups are both unsubstituted); or

(ii) R² represents H or C₁₋₄ alkyl and R⁴ represents H or C₁₋₅ alkyl, then

(i) R³ does not represent:-

methyl;

C₂₋₁₀ alkyl or C₄₋₁₀ alkenyl, both of which are substituted at the 2-, 3- or 4-C position by -W-A¹-N(R^{6b})(R^{6c}) and which alkyl group only is also optionally substituted at the 3- to 10-C, 4- to 10-C

or 5- to 10-C position (respectively) by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl; or C₁₋₄ alkyl, which alkyl group is terminally substituted by -W-A¹-N(R^{6b})(R^{6c}), and is also optionally terminally substituted by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl; in which, in both cases, W is a single bond, A¹ is a single bond or C₁₋₃ alkylene, R^{6b} or R^{6c} is H or unsubstituted C₁₋₁₀ alkyl and R^{6b} or R^{6c} (as appropriate) is H, C₃₋₈ cycloalkyl, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, phenyl or C₁₋₃ alkylphenyl (which latter five groups are all unsubstituted); or

(II) R³ does not represent:-

C₁₋₁₀ alkyl or C₃₋₁₀ alkenyl, both of which are substituted at the 1- to 5-C (as appropriate) by unsubstituted C₁₋₆ alkoxy carbonyl or W-A¹-N(R^{6b})(R^{6c}) and which alkyl or alkenyl groups are also optionally substituted at the 2- to 10-C, 3- to 10-C, 4- to 10-C or 5- to 10-C position (respectively) by unsubstituted C₃₋₈ cycloalkyl or unsubstituted phenyl; or C₁₋₅ alkyl, which alkyl group is terminally substituted by an unsubstituted C₁₋₆ alkoxy carbonyl group or -W-A¹-N(R^{6b})(R^{6c}), and is optionally terminally substituted by unsubstituted phenyl or unsubstituted C₃₋₈ cycloalkyl;

in which, in both cases, W is -C(O)-, A¹ is a single bond, R^{6b} or R^{6c} is H or unsubstituted C₁₋₃ alkyl and R^{6b} or R^{6c} (as appropriate) is H, C₁₋₁₀ alkyl, C₃₋₁₀ alkenyl, C₃₋₈ cycloalkyl, phenyl, C₁₋₃ alkylphenyl (which latter five groups are all unsubstituted), linear C₁₋₄ alkyl (which latter group is terminally substituted by amino), or R^{6b} and R^{6c} together represent unsubstituted C₃₋₅ alkylene;

(c) when R¹ and R² both represent methyl and are in the mutually *trans*-configuration and R⁴ represents H or C₁₋₄ alkanoyl, then R³ does not represent:-

unsubstituted C₁₋₈ alkyl;
unsubstituted C₃₋₈ alkenyl;
unsubstituted C₃₋₈ alkynyl;

C₁₋₆ alkyl, terminally substituted by an unsubstituted C₃₋₈ cycloalkyl group; C₁₋₃ alkyl, terminally substituted by C₃₋₈ cycloalkanoyl, C₃₋₈ cycloalkoxy, C₃₋₈ cycloalkyl, naphthyl, thiophenyl, thiophenoxy, furanyl, furan-oxo, tetrahydrofuranyl, pyridinyl or pyridinyloxy (which latter eleven groups are all unsubstituted), phenyl or phenoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy); or

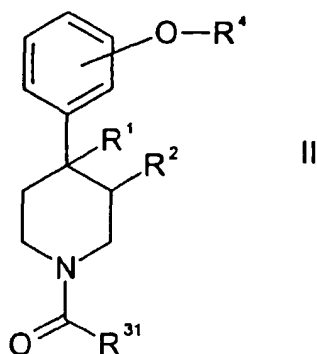
C₁₋₄ alkyl, terminally substituted by an OH group and by one of the following groups: phenyl (which latter group is optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy), C₁₋₂ alkylphenyl, C₃₋₈ cycloalkyl, thiophenyl, furanyl or pyridinyl (which latter four groups are all unsubstituted);

in all of which provisos, optionally substituted alkyl, alkenyl and alkynyl groups are not interrupted by one or more O and/or S atoms.

2. A compound as claimed in Claim 1, wherein the group OR⁴ is attached to the benzene ring in the position *meta*-relative to the piperidine group.
3. A compound as claimed in Claim 1 or Claim 2, wherein R¹ represents C₁₋₂ alkyl.
4. A compound as claimed in any one of Claims 1 to 3, wherein R² represents H or C₁₋₂ alkyl.
5. A compound as claimed in any one of Claims 1 to 4, wherein R³ represents aryl (optionally substituted by one or more substituents selected from C₁₋₂ alkyl, C₁₋₂ alkoxy, halo, nitro and -N(R^{5a})(R^{5b})), C₁₋₈ alkyl, C₃₋₈ alkenyl or C₃₋₈ alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally interrupted by one or more oxygen atoms and/or are substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, CN, halo, C₁₋₄ alkoxy carbonyl, C₄₋₆ cycloalkyl, C₅₋₇ cycloalkanoyl, Het¹, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C₁₋₂ alkyl, C₁₋₂ alkoxy or halo), or -W-A¹-N(R^{6b})(R^{6c}).
6. A compound as claimed in any one of Claims 1 to 5, wherein W represents a single bond or C(O).
7. A compound as claimed in any one of Claims 1 to 6, wherein A¹ represents a single bond or C₁₋₃ alkylene.

8. A compound as claimed in any one of Claims 1 to 7, wherein R^{5a} to R^{5d} each independently represent H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{4-8} cycloalkyl, C_{1-2} alkylphenyl, aryl or Het².
9. A compound as claimed in any one of Claims 1 to 8, wherein R^{6b} and R^{6c} independently represent H, C_{1-2} alkyl, Het³, or R^{6b} and R^{6c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O or S and is optionally substituted by one or more C_{1-2} alkyl groups.
10. A compound as claimed in any one of Claims 1 to 9, wherein Het¹, Het² and Het³ independently represent 5- to 7-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O and C_{1-2} alkyl (which latter group is optionally substituted by one or more halo atoms).
11. A compound as claimed in any one of Claims 1 to 10, wherein R^4 represents H or C_{1-5} alkanoyl.
12. A compound as defined in any one of Claims 1 to 11, for use as a medicament.
13. A compound as defined in any one of Claims 1 to 11, for use as an animal medicament.
14. A formulation comprising a compound as defined in any one of Claims 1 to 11, in admixture with a pharmaceutically, or a veterinarily, acceptable adjuvant, diluent or carrier.
15. A formulation as claimed in Claim 14, which is a veterinary formulation.
16. The use of a compound as defined in any one of Claims 1 to 11, in the manufacture of a medicament for the curative or prophylactic treatment of pruritus.
17. A method of treating or preventing pruritus, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 11, to a patient in need of such treatment.
18. A process for the preparation of a compound as defined in Claim 1, which comprises:

a) for compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified in Claim 1 in respect of R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom via a CH_2 group, wherein Het¹ is as defined in Claim 1, reduction of a corresponding compound of formula II,



wherein R^{31} represents H, C_{3-8} cycloalkyl, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN , $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)),

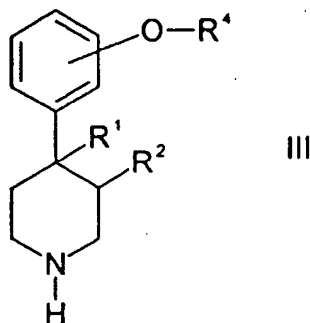
C₁₋₉ alkyl, C₂₋₉ alkenyl or C₂₋₉ alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{5c}, S(O)_nR^{5d}, CN, halo, C₁₋₆ alkoxy carbonyl, C₂₋₆ alkanoyl, C₂₋₆ alkanoyloxy, C₃₋₈ cycloalkyl, C₄₋₉ cycloalkanoyl, N(R^{6a})S(O)₂R⁷, Het¹, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH₂CN, CONH₂, C₁₋₄ alkyl, C₁₋₄ alkoxy and C₁₋₅ alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A¹-N(R^{6b})(R^{6c}), and R¹, R², R⁴, R^{5c}, R^{5d}, R^{6a} to R^{6c}, R⁷, Het¹, n, W and A¹ are as defined in Claim 1;

b) for compounds of formula I in which R⁴ represents C₁₋₁₂ alkanoyl, (pyridin-3-yl)carbonyl or (pyridin-4-yl)carbonyl (which latter two groups are optionally in the pyridine N-oxide form), reaction of a corresponding compound of formula I in which R⁴ represents H with a compound of formula V,



or a suitable derivative thereof, wherein R⁴¹ represents C₁₋₁₁ alkyl, pyridin-3-yl or pyridin-4-yl (which latter two groups are optionally in the pyridine N-oxide form);

c) reaction of a corresponding compound of formula III,



wherein R¹, R² and R⁴ are as defined in Claim 1, with a compound of formula VI,



wherein L¹ represents a leaving group and R³ is as defined in Claim 1;

d) for compounds of formula I wherein R³ represents C₁ alkyl, which, in place of being optionally substituted by the substituents as defined in Claim 1, is instead optionally substituted by R³¹, wherein R³¹ is as defined above, reaction of a corresponding compound of formula III, as defined above, with a compound of formula VII,



wherein R³¹ is as defined above, in the presence of a suitable reducing agent;

e) for compounds of formula I wherein R³ is a C₁₋₁₀ alkyl, C₄₋₁₀ alkenyl or C₄₋₁₀ alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R³ group is substituted at 2-C (relative to the piperidine N-atom) by S(O)R^{5d}, S(O)₂R^{5d}, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, -C(O)-A¹-N(R^{6b})(R^{6c}), -S(O)-A¹-N(R^{6b})(R^{6c}), or -S(O)₂-A¹-N(R^{6b})(R^{6c}), wherein R^{5d}, R^{6b}, R^{6c} and A¹ are as defined in Claim 1, reaction of a corresponding compound of formula III, as defined above, with a compound of formula VIII,



wherein R^{3a} represents R³ as defined in Claim 1 except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents S(O)R^{5d}, S

(O)₂R^{5d}, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, -C(O)-A¹-N(R^{6b})(R^{6c}), -S(O)-A¹-N(R^{6b})(R^{6c}) or -S(O)₂-A¹-N(R^{6b})(R^{6c}), wherein R^{5d}, R^{6b}, R^{6c} and A¹ are as defined in Claim 1;

f) conversion of one functional group on an alkyl, heterocyclic or aryl group in a compound of formula I to another.

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19. A compound of formula II, as defined in Claim 18.

20. A compound of formula III, as defined in Claim 18.

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(19)



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(11)

EP 1 072 595 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
14.02.2001 Bulletin 2001/07

(51) Int Cl.⁷: C07D 211/22, A61K 31/445,
A61P 17/04, C07D 405/06,
C07D 401/06

(43) Date of publication A2:
31.01.2001 Bulletin 2001/05

(21) Application number: 00304226.4

(22) Date of filing: 18.05.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 28.05.1999 GB 9912415

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GB

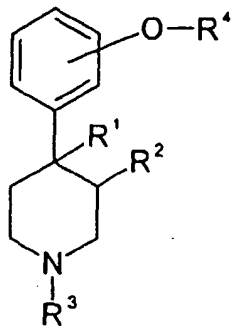
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(54) **4-arylpiperidine derivatives for the treatment of pruritus**

(57) There is provided a compound of formula I,

wherein R¹, R², R³ and R⁴ have meanings given in the description, which are useful in the prophylaxis and in the treatment of pruritus.

**EP 1 072 595 A3**



European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 00 30 4226

DOCUMENTS CONSIDERED TO BE RELEVANT			
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			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D A61K A61P
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		17 November 2000	De Jong, B
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPC FORM 1503 03.82 (P04C07)



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INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 30 4226

Although claim 17 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compounds.

Claim(s) searched completely:
16,17

Claim(s) searched incompletely:
1-15,18-20

Reason for the limitation of the search:

Present claims 1-15, 18-20 relate to an extremely large number of possible compounds. Support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples and closely related homologous compounds.



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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 30 4226

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 30 4226

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

17-11-2000

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